ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 18, Number 6 NOVEMBER-DECEMBER, 1934 Serial No. 98

THE HUMAN CORPUS LUTEUM AND PROGESTIN*

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DETROIT

The opening of the eighteenth annual session of the Association for the Study of Internal Secretions is another landmark in the progress of correlation of the brilliant laboratory achievements with their clinical applications in the field of endocrinology. This is an occasion when individuals and groups widely scattered geographically and having a diversity of special interests assemble for the integration of ideas related to the problems which they share in common. It is a clearing house for presentation of facts, interpretation of experimental data, discussion of theories, and comparison of opinions. This Association marks the intersection of the numerous avenues of approach to the problem of endocrinology. Here controversies may be aired with reasonable hope of arriving at satisfactory agreement. A profitable supplement to the annual program would be a clinical symposium for demonstration of the practical achievements of endocrinology in the recent past.

The scope of the relationship of the glands of internal secretion to each other and to the whole organism is so extensive that individual effort and collective coöperation is essential for elucidation of the questions involved. The more complex the problem, the greater is the need for intelligent coöperation. A comparison of recent programs of this Association as well as other societies, illustrates the growing tendency toward coöperative efforts. A study of the various combinations of the specialties represented in the different groups is enlightening.

The increasing tendency to specialization for the past quarter century holds more than passing interest. This applies to the scientific as well as to the clinical branches of medicine. One may ask whether or not this diversification and concentration in separate fields may be in accordance with the biological law that—early specialization and over-specialization threaten extinction. It is within our power, however, to control the extent of specialization sufficiently to preserve integrity. Controlled specialization of the various phases of endocrinology has become a necessity since the

*Presidential address, read before the Eighteenth Annual Meeting of the Association for the Study of Internal Secretions, Cleveland, Ohio, June 11, 1934.

accumulated knowledge related to the whole field is so great that a single mind cannot comprehend all details. Therefore, the coöperative efforts of many individuals and groups must be integrated to amplify the various phases of the subject and at the same time maintain a proper balance.

This Association is fortunate on account of the unique position which it occupies as a clearing house for the endocrine problems with which the clinical and non-clinical specialties are confronted. In separate sessions the anatomists, physiologists and chemists contribute to our knowledge of endocrinology from the perspective of the basic sciences. Facts are established from animal experimentation which permit plausible deductions for human applications. In the clinical societies the perspective shifts until we find ourselves in a situation not unlike that described by John G. Saxe in "The Blind Men and the Elephant." The First approached the Elephant and found his broad and sturdy side very like a wall. The Second found his tusk like a spear. The Third admitted that his squirming trunk was quite like a snake. The Fourth thought his knee not unlike a tree. The Fifth perceived the ear to be like a fan, while the Sixth compared the tail to a rope.

The intelligent laity are eager to obtain authentic information concerning endocrinology as it may affect them. In this regard they are most fortunate and deeply indebted to one of our charter members and a pillar of the organization—R. G. Hoskins, whose "Tides of Life" (1) elucidates this large and difficult subject in a fascinating and informative manner. His contribution meets a long-felt need and serves to counteract the vicious claims of unscrupulous advertisers.

The physician who has only a general interest in endocrinology may also be perplexed when confronted by the vast literature relating to the many phases of this subject. Not the least of his difficulties is experienced when he tries to decipher the rather complex terminology, contradictory and confusing as it often is; e.g., the numerous terms applied to the follicular hormone and also the numerous functions that have been attributed to the pituitary gland, many of which are purely theoretical and founded on insufficient fact. A text-book on so rapidly changing a subject must soon be out of date; therefore, a well-informed reader must depend upon current literature. Shall this organization accept the challenge to clarify the terminology?

Every clinical specialty encounters symptoms and conditions which are undoubtedly due to aberration of functions of the glands of internal secretions. The astute physician is ever alert to determine to what extent the lessons learned from animal behavior are applicable to clinical problems.

The laboratory worker accepts a problem, propounds a theory, and devises a series of experiments to prove or disprove his theory. The results obtained from one species may be checked by comparison with other species. Normal animals in sufficient numbers of desirable age, weight, and maturity may be selected. The clinician, however, has great difficulty in determining

normals although he has an abundance of material illustrating aberrations of functions. For obvious reasons, the normal individual cannot be kept under the same careful and continued observation as the abnormal.

Not infrequently while a patient is narrating symptoms, it is evident that the narrator has had previous experiences, seemingly unimportant to her, which would have been very impressive to a trained observer. Thus a chapter or chapters have been written and concluded without a single scientific observation having been made: only end results remain.

At the first contact between patient and physician, a new chapter is opened which would be vastly more intelligible if the preceding chapters were accurately known. This point may be illustrated by reference to the problems of maturity. For instance, an adolescent girl complains of abnormal menstruation which to her is the first conspicuous sign of abnormality. When further subjective data are obtained from the patient and her family, and the objective findings are added, it may be obvious that in earlier life the function of the pituitary gland had been disturbed. But the period of disturbed activity is over and although the manner of action is known only by speculation, it is now obvious that maturity has been delayed. It seems quite likely that the end result of this delayed maturity continues into later life with resulting lowered fertility and relative sterility until an age much beyond the average.

The patient's prime interest is to obtain relief from annoying symptoms while to the physician this may seem the least important part of the problem. It becomes his duty, therefore, to seek for the cause of the disturbance and to inform the patient of the nature of the disability in order that coöperation may be established. This may entail rather extensive studies to determine the variations from the normal in the past. It must be determined whether the cause is organic or functional. The organic changes have long been treated with reasonable success, but many of the functional disturbances still remain enigmas. For this reason, the conscientious physician must inform himself of advances in other spheres which bear on his particular problems. Critical judgment in so wide a field is difficult, so he turns to summaries by various authorities.

One of the outstanding sources of error in applying the scientific data to the human problem is the unfortunate tendency to plausible inferential analogy. Furthermore, general statements made without accurate reference to the species concerned are misleading. A vicious circle is formed which includes the gullibility of the public stimulated by sensations of the press and pseudo-scientific publications as well as the attractively alluring but sound products of the laboratory. Meanwhile, the physician finds himself an intermediary attempting to translate the scientific facts into suitable form for popular consumption. Let us illustrate further the possible errors of inferential analogy: With the discovery that follicular fluid will substitute for the ovaries in castrated rats and mice, and when injected into such animals will reproduce a complete oestrous cycle, it is quite natural to infer that the same fluid being present in human ovaries can substitute in cas-

trated females to produce a complete sexual cycle. The fallacy of this analogy lies in the dissimilarity existing between the primate menstruation and the oestrus of animals, spoken of collectively as the sexual cycle. To include under one name two things which have only a partial resemblance makes it very much more difficult to understand either of them.

Fancy rather than fact has led to quite extensive employment of extracts of follicular fluid to counteract the abnormal tendencies in menstrual cycles with disappointing consequences. The public being made aware of the striking results obtained in the laboratory by substituting extracts for ovaries, have besought their physicians for aid in this direction. With the best intentions, the uninformed physician, the intermediary, may share with the public in this gullibility due to lack of opportunity to inform himself fully concerning the actual status of newer forms of proposed therapy. Relief of symptoms coincident with the administration of various extracts of follicular fluid has been accepted as convincing evidence of the efficacy of the product. A false confidence is established which is often hard to shake and the truth is reluctantly accepted. This method of trial and error, however, is not without benefit to the problem as a whole, because it has disclosed some of the fallacies of applying deductions from the behavior of one species to another.

At the close of the last century the stimulating theory of Prenant and von Born that the corpus luteum is a gland of internal secretion established the foundation for a large number of experiments and theories. Early in this century Fraenkel, a vociferous exponent of von Born's theory, cauterized the corpus luteum in rabbits and removed the corpus luteum from patients at operation. Some rather sweeping deductions were drawn which were responsible for the production of a wide variety of preparations of the corpus luteum for human administration, most of which are now known to be inert. In 1917 Mulon (2) enumerated 26 different functions which had been credited to the corpus luteum. This number could be greatly extended if one could add the wide variety of clinical applications which have been made. The coincidences in the improvement of symptoms and the psychotherapeutic results obtained when corpus luteum preparations have been administered, have been so frequent that conviction of their merits as a curative agent has been well founded in fancy but not in fact.

Among all the functions attributed to the corpus luteum only a few were founded on a factual basis. One of the oldest conceptions that the corpus luteum provides a satisfactory manner of healing the ruptured follicle with a minimal scar is well-founded and generally accepted. The elaboration of a hormone identical with the follicular hormone has been shown quantitatively and qualitatively in numerous species, including the human. There is again wide species variation, for all animals do not produce the follicular hormone in the corpus luteum. A second hormone elaborated by the corpus luteum has been satisfactorily demonstrated by Corner (3), who first extracted progestin from the corpus luteum of the sow and by injection into castrated rabbits produced typical progestational

proliferation of the endometrium. Since Corner's brilliant work, which has been confirmed by others, the alluring possibility of the human corpus luteum functioning in a similar manner has attracted wide attention. By inferential deduction it has been assumed that the human corpus luteum also elaborates progestin. Many statements appear in the literature concerning the activity of progestin without reference to the species so that a casual reader might well infer that progestin has been proved to be a factor in the human sexual cycle.

The assumption of von Born that the corpus luteum performs an important function in the nidation of the fertilized ovum and the development of the embryo has been found correct for many species. Drips (4) found that removal of both ovaries at any time during gestation produced abortion in the 13-lined ground squirrels. Harris (5) found that bilateral oophorectomy always produced resorption or abortion in pregnant mice. On the other hand, Loeb and Hesselberg (6) found that castration of pregnant guinea pigs was not always followed by abortion. In the human, gestation may continue successfully even though the corpus luteum is removed very early in pregnancy. In one case (7) it was removed as early as the 21st day of the cycle, that is, a few days after the probable time of fertilization of the ovum. Several cases are recorded in which the ovaries were removed during the first trimester of pregnancy without interrupted gestation. These citations show wide species variations in the importance of the function of the corpus luteum for gestation.

Demonstration of the possibility of the elaboration of progestin by the human corpus luteum may be approached in two ways: (1) The substitution of an extract in castrates; (2) the extraction of progestin from human corpora lutea. Some claims have been made for the first method. Kaufmann (8) reported a menstrual bleeding in a 22-year-old woman who had been castrated five years previously for dermoid cysts. She had complete amenorrhea for five years. Following the administration of 320,000 m.u. of progynon benzoate and 90 rabbit units of corpus luteum she had what he considered to be a typical menstrual bleeding. Twenty cc. of uncoagulated blood was collected during the first 24 hours. The bleeding lasted 68 hours altogether. Some menstrual mucosa was cast off with the bleeding. Curettings removed 38 hours after the onset of bleeding showed pregravid mucosa. The author advises further careful experiments before recommending a practical application.

Loeser (9) reported concerning a 28-year-old woman with primary amenorrhea, although evidence was lacking to establish that it was true menstruation. He reports two other cases in which follicular hormone and corpus luteum hormone were given after which the patients menstruated for six days. His claim for a true menstruation was based upon a microscopical report of curettings removed on the second day of the flow. According to Meyer, who reviewed the specimen, the material was scant and not of uniform structure. Places were found with typical structure of pre-gravid glands with good glycogen production.

Clauberg (10) in 1933 mentions some experiments for attempting to extract corpus luteum hormone from blood. Amounts of 230 to 335 cc. taken during and after menstruation gave negative tests for luteal hormone. Direct injection of 75 cc. of serum from patients in early pregnancy gave negative results. Three hundred cc. of blood from patients early in pregnancy showed no luteal hormone. He gives the method of extraction of the hormone from human corpora lutea but does not state that he tested the extract for the presence of that hormone.

In view of the importance of obtaining positive information as to the presence of progestin in the human corpus luteum, a coöperative study was undertaken in 1933 to determine, if possible, the presence of this hormone.*

The scarcity of material makes it almost prohibitive for one individual to carry out the experiment single-handed. Even with the combined efforts, several months elapsed before sufficient material was collected for the first test.

MATERIAL

Fresh specimens of normal corpora lutea were taken at the operating table and preserved in 95 per cent alcohol, care being taken not to allow much air space above the surface level of the alcohol. This is equivalent to the first stage in the extraction as in the experiments of Corner, 95 per cent alcohol was used. The length of time consumed in collecting the material may have affected the potency of the product but it has been shown that in alcoholic solutions progestin obtained from the corpus luteum of the sow is stable for a long period of time. In the first series 58 corpora were obtained. The ages of the patients from which these were obtained were as follows:

	Cases
Under 20	4
Between 20 and 30	18
Between 30 and 40	24
Over 40	10
Unknown	2
	58

Corpus luteum of pregnancy including ectopics and 1 hydatidiform mole	11
Corpora removed from the 1st to 14th day	14
The stage in the cycle not determined	4
Known to be removed in the latter half of the intermenstruum	29

The source of material is tabulated in detail because in this series there was quite a wide variation in the conditions of the individual from which the corpus was obtained. In the second series there were 18 specimens, all of which were collected during the second half of the intermenstruum. The total weight of the preserved tissue in the first series was 94 grams and in the second series 37.5 grams.

The material was chopped fine and extracted in the same alcohol used for preservation. A progestin extract was made in accordance with the

*This coöperative problem of determining the presence of progestin in the human corpus luteum was begun in May, 1933, by a group composed of Dr. John C. Burch of Vanderbilt U. School of Medicine, Nashville, Tenn., Dr. E. C. Hamblen, Duke U., Durham, N. C., Dr. Oliver Kamm, Mr. D. A. McGinty, and Dr. J. P. Pratt, of Detroit.

method of Allen (11), although it was carried only to the stage of the "crude oil" in order to avoid loss of activity in the latter steps of the concentration process. In the first lot the theelin was not separated. The final product was dissolved in 95 per cent alcohol, each cc. corresponding to 5 grams corpus luteum tissue and supplied for assay under No. 3455G. At the same time, an extract of fresh hog corpora lutea was made and submitted under test No. 3454G.

The assay method used was as follows:

In the Corner-Allen rabbit assay method for progestin, estrus rabbits are used. In order to make sure that they are in estrus, copulation with a male is essential. Within a few hours after copulation the rabbits are ovariectomized and progestin is injected, beginning the same day of ovariectomy for 5 days. Uterine sections are removed on the 6th day after ovariectomy.

In the method used here, theelin was given twice or three times a day for two days in order to bring about estrus in younger rabbits or to make certain of it in older ones. Sixty hours after the start of theelin injections, Antuitrin-S was given intravenously (1 cc.) to induce ovulation, corpus luteum formation, pseudopregnancy and uterine progestation reactions, in the non-ovariectomized rabbits. This procedure serves as a positive control and the results are identical with positive controls used in the Corner-Allen method, in which estrous females are mated with vasectomized bucks.

In rabbits to be used for progestin assay, ovariectomy is performed 15-20 hours after Antuitrin-S injection, progestin injections being started immediately and continued as in the Corner-Allen method.

PROGESTIN ASSAYS

Extract Number	Dose in Terms of Weight of Gland Used	Result
No treatment	Control rabbit (overiectomized)	Negative
No treatment	Control rabbit (normal)	Positive
3454G (hog)	20 gm	Negative
3454G (hog)	27 gm	Positive*
3455G (human)	5 gm	Negative
3455G (human)	15 gm	Negative
3455G (human)	25 gm	Negative

*Previous work has shown that positive responses are usually obtained in the region 20 ± 5 gm.

In view of the negative results in the progestin tests on Extract No. 3455G a part of this extract was taken through the Allen and Meyer (12) process for separation of progestin from theelin. In addition, another lot of human corpora lutea more recently collected weighing 37.5 grams were studied by the methods referred to above and taken through the process for separation of theelin.

THEELIN ASSAY ON PROGESTIN EXTRACT

In view of the fact that the presence of the ovarian follicular hormone has been shown to interfere with progestin evaluation and in view of the fact that the human corpus luteum has been shown to contain considerable ovarian hormone (13) an assay for theelin content was made on extract No. 3455G. The results were positive at levels of 2, 5 and 10 Doisy rat units per cc., thus demonstrating a considerable amount of theelin to be present. The upper limit was not determined but it is obvious that in the largest of the above doses 50 or more units of theelin had been administered.

Extract Number	Dose in Terms of Weight of Gland Used	Result
No treatment	Control rabbit (with intact ovaries)	Positive
No treatment	Control rabbit (ovariectomized)	Negative
34,525G (human)	10 gm	Negative
34,525G (human)	25 gm	Negative
34,525G (human)	40 gm	Negative

DISCUSSION

These preliminary experiments undertaken to demonstrate the presence of progestin in the human corpus luteum do not permit drawing any final conclusions, although a total of 131.5 grams of human corpus luteum was extracted for progestin by the Corner-Allen method. The first lot was obtained at varying times in the menstrual cycle and during early pregnancy. The second lot was taken only during the last half of the intermenstruum. Before assay for progestin this lot was freed from theelin. As a control the extraction and assay of the human corpora lutea were paralleled by similar procedure with hog corpora lutea. The results obtained from the hog corpora lutea confirmed previous reports yielding progestin in 20 ± 5 grams of material. The human corpora lutea were negative up to 40 grams.

It may be necessary to limit the time of collection of material to a particular period in the cycle. Furthermore, progestin from the human corpus luteum may not be stable for so long a period as the material from the hog. Perhaps progestin is present in other portions of the ovary than the corpus luteum. Experiments are now in progress to determine these possibilities. At present the results should make one hesitate to theorize that the human corpus lutum is entirely analogous to the material obtained from hogs in regard to its progestin content. It is known that they differ in theelin content and that the origin of the lutein cells differs in the two species.

SUMMARY

The brilliant achievements in the laboratory have stimulated physicians to make practical application to the endocrine problems of patients. The variable response according to species necessitates caution in assuming by analogy that results may be anticipated in the human similar to those demonstrated in animals. As an illustration of species variation the function of the corpus luteum is cited. In some animals its presence is required throughout gestation. In others its presence is required for varying lengths of time while in the human gestation has progressed normally in the absence of corpus luteum except for a very few days at the beginning of pregnancy.

Two hormones have been extracted from the corpus luteum of animals, the estrogenic substance and progestin. The presence of progestin first extracted from the corpus luteum of the sow has not been demonstrated in many species. Since its presence has not been shown in the human corpus luteum, an attempt was made to demonstrate it in corpora lutea taken at operation and preserved immediately in 95 per cent alcohol. A total of 131.5 grams of human corpus luteum was obtained and the Corner-Allen method of extraction of progestin was applied to this material. The assay of the human material was paralleled by similar product from the sow. In the sow, tests for progestin are positive in 20 ± 5 grams of material. The human material gave negative results up to 40 grams, therefore not highly concentrated. While these preliminary experiments do not demonstrate the presence of progestin in 40 grams or less of human corpora lutea, they

would seem to indicate that progestin is, at least, not as plentiful in human as in hog corpora lutea or that its presence is confined to certain times in the cycle not yet determined.

Attention is also called to the difference in theelin content in corpora lutea from different species. Theoretical assumption of the presence of progestin in the human corpus luteum needs the support of positive demonstration of such a product.

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THE INTERRELATIONSHIP OF THE ADRENAL CORTEX AND THE ANTERIOR LOBE OF THE HYPOPHYSIS*†

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ANATOMICAL CONSIDERATIONS

The Adrenals in Hypophysectomized Animals and in Hypopituitarism. That a very intimate relationship exists between the adrenal cortex and the anterior lobe of the hypophysis has been suspected from both clinical and experimental observations. It has been very definitely established that a rapid and extensive atrophy of the adrenal cortex follows total hypophysectomy in the tadpole (1, 2), rat (3, 4, 5, 6, 7, 8, 9), rabbit (10, 11), and dog (12, 13, 14).

The histological changes in the adrenals of rats have been carefully studied by Smith (5). The medulla appears normal. The cortex, which is probably solely responsible for the diminution in the size of the gland, is altered in a pronounced way. The cells of all three zones show diminution in cytoplasm, but are not decreased in number. Fat deposits are limited to a central zone. In our hypophysectomized rats we have found the same changes. To determine the site of the initial alterations of the adrenal glands, eighteen totally hypophysectomized rats were examined at varying postoperative periods.‡ Five days after hypophysectomy the gland showed minimal histological changes. There was some distortion of the reticular zone, and the cells in this layer and in the inner part of the fascicular zone were smaller than normal. At eight days the reticular zone was hardly recognizable and the fascicular layer showed more marked changes. Thereafter the atrophy was progressive until the entire cortex was involved, and the fascicular zone presented no semblance of its normal cord-like arrangement of cells. This is, in general, the sequence of events which Houssay and Sammartino (12) have observed in the dog.

Smith (4, 5) has demonstrated that these atrophic adrenals can be restored to their normal histology and to normal or near-normal weight by daily homotransplants of the pituitary gland. Evans and his co-workers (8) also claim to have restored the glands more or less completely with potent extracts of the growth hormone. Prolan is ineffective in this respect. Collip, Anderson, and Thompson (15) report a potent adrenotropic fraction of the anterior lobe hormone which they state will repair the adrenals without inducing growth in hypophysectomized rats.

*Aided by a grant from Mr. Stephen C. Clark.

†Read before the Eighteenth Annual Meeting of the Association for the Study of Internal Secretions, June 12, 1934, Cleveland, Ohio.

‡We have used a modification of Smith's parapharyngeal operation. In all of our experiments proof of completeness of extirpation has been obtained by serial sections of the sella.

There is considerable clinical evidence agreeing with the experimental in reference to adrenal cortical atrophy in pituitary deficiency. Falta (16), Cushing and Davidoff (17), Mackenzie (18), and Jaffe and Tanenberg (19) have reported various atrophic lesions of the pituitary with evidence of hypofunction which were accompanied by extensive atrophy of the adrenal cortex. In pituitary dwarfism the adrenals are described as very small, sometimes with hypoplastic changes in the cortical layers, as Erdheim (20), Kraus (21), Priesel (22), and Simmonds (23) have demonstrated. In Simmonds' pituitary cachexia the adrenal glands are small, although frequently histologically normal (24, 25, 26, 27). In anencephalia the hypophysis is sometimes absent, and when present shows varied marked structural abnormalities, and the adrenal glands present a striking cortical atrophy. That the latter change is dependent upon the former is the opinion of a number of investigators. Houssay (14) has recently reviewed the subject.

The Adrenals in Experimental and Clinical Hyperpituitarism. The growth hormone of the anterior lobe of the hypophysis is reported to induce hypertrophy of the adrenal cortex. As early as 1909 Delille (28) observed adrenal cortical hypertrophy following the injection of pituitary extract. Evans (29) states that the adrenals of rats treated with the growth hormone are distinctly larger than normal. Cushing and Teel (30) and Teel and Cushing (31) mention hypertrophy of the adrenals as part of the picture produced in growth-hormone treated dogs. Putnam, Benedict, and Teel (32) observed adrenal cortical hyperplasia and microscopic cortical adenomata in a dog treated for fourteen months with growth hormone. Bauman and Marine (33) likewise found hypertrophy of the adrenal cortex in treated rabbits. It is unfortunate that these investigations were not controlled by inactivated pituitary extracts.

Clinically, numerous observers have found adrenal cortical hypertrophy in acromegaly. It is true that Marie and Marinesco (34) in their interesting case described slightly atrophic adrenals. Hyperplasia of the cortex is, however, the usual finding. Fischer (35), Schultze and Fischer (36), Kraus (37), Cushing and Davidoff (17), and others have reported cases. In one of them (36) the adrenals weighed 57 grams. In addition, adenomata of the adrenal cortex are not infrequently encountered in acromegaly, in which cases the adrenals may reach enormous size (Gauckler and Roussy (38), Kiyono (39), Cushing and Davidoff (17).

Cushing (40) has recently discussed the possible occurrence of secondary adrenal cortical hypertrophy as a result of basophilic adenomata of the hypophysis. There is no experimental basis for such an assumption, and indeed, in the three definitely proved cases of basophilic adenomata, which Cushing includes in his review, no definite adrenal alterations were found, except a possible slight enlargement in one (Teel, 41).

Failure of Compensatory Hypertrophy in Hypophysectomized Rats. The remarkable capacity of the adrenal gland to undergo compensatory

hypertrophy when part of the gland is removed is well known. In fact, this has been one of the difficulties which investigators have met with in the field of adrenal physiology, for if, in performing a bilateral adrenalectomy a tiny, possibly microscopic, remnant is left, this undergoes such a marked hyperplasia that the animal survives and presents at autopsy a well-formed gland at the operative site (42). Collip, Anderson, and Thompson (9) state that if one adrenal is removed from an hypophysectomized rat, the second fails to undergo compensatory hypertrophy and remains atrophic. Evans and his co-workers (8) report that restoration of the atrophic adrenals can be brought about only if therapy with anterior lobe preparations is instituted soon after hypophysectomy, and is exceedingly difficult if enough time elapses after the operation so that the glands are markedly atrophic before therapy is begun.

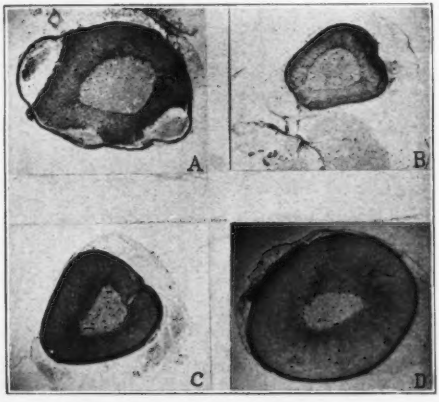

Figure 1. Effect of hypophysectomy on the adrenal glands. A—Adrenal gland removed at time of total hypophysectomy. B—Contralateral atrophic adrenal, 27 days later. C—Adrenal gland removed at the time of incomplete hypophysectomy. D—Contralateral hypertrophic adrenal, 27 days later. Magnification, 22.

We have, consequently, studied this problem, removing the first adrenal at the time of hypophysectomy, and leaving a structurally normal gland. Six rats were totally hypophysectomized and unilaterally adrenalectomized. They were sacrificed after an interval of from eighteen to thirty days. In every case at autopsy the remaining adrenal showed the typical cortical atrophy found in hypophysectomized animals. Three partially hypophysectomized and unilaterally adrenalectomized rats served as controls. At autopsy the remaining gland in each of them was hypertrophic (Figure 1).

The Pituitary Gland in Experimental and Clinical Adrenal Insufficiency. In many of the pathological reports of Addison's disease, description of the pituitary gland is lacking. A number of careful studies, however, indicate that, in this disease, the hypophysis undergoes striking alterations. Kraus (26, 43, 44) has studied seven cases of Addison's disease, and two additional cases of adrenal cortical atrophy without the usual

Addisonian symptoms. In general, he finds marked diminution in the number of normal basophiles. Most of the basophiles present show irregularity, indistinct borders, small size, pyknosis. They are not normally granular. In one case no normal basophiles were present. The eosinophiles are diminished in number in some cases and in all show certain changes—atrophy, pyknosis, and irregular outlines. The chief cells are increased. Many of these are smaller than normal and pyknotic. Guizzetti and Reggiani (45) found a complete disappearance of basophiles with increase of chromophobes. Berblinger (46, 47) has studied four cases, finding no changes in the pituitary of one, slight diminution in basophiles in one, and very marked decrease in the number of normal basophiles in two. He considers the alterations in the basophiles the characteristic pituitary finding of Addison's disease. Terplan and Sanes (48) have recently reported a cortin-treated case of Addison's disease which showed dilatation of the capillaries of the pituitary, normal number of chromophobes and eosinophiles (which were slightly atrophic), and decrease in the number of basophiles. Some showed degenerative changes, small eccentric nuclei, sometimes pyknotic, large cell body, coarsely granular, indistinct cell outlines. Whereas there is general agreement in the pituitary findings in clinical adrenal insufficiency, the literature dealing with the histological changes in the hypophysis occurring after adrenalectomy in animals is exceedingly confusing and contradictory (49, 50, 51, 52, 53). It is probable that some of the discrepancy in these findings is attributable to the degree of completeness of the operation. It is not unexpected that it should prove difficult to reproduce experimentally the pathological picture of the pituitary in Addison's disease, since completely adrenalectomized animals survive for such a short period of time. If such animals are treated inadequately with the cortical hormone, however, they may be kept alive indefinitely and in a state of chronic insufficiency.

The pituitary of one female dog which was completely adrenalectomized under spinal anesthesia, and maintained in a state of chronic adrenal insufficiency with inadequate doses of the cortical hormone for one hundred days, and which finally died with typical symptoms of adrenal deprivation after twenty-eight days of no treatment, was examined for us by Dr. Kindell, of the Department of Pathology. He found a picture strikingly like that reported in clinical Addison's disease. There was an increase in vascularity and a complete disappearance of basophiles.

Corey and Britton (54) claimed that in young rats their adrenal cortical hormone produced hypertrophy of the anterior lobe. Their evidence, however, does not bear out their claims.

THE GROWTH FACTOR, TEMPERATURE, ACTIVITY, AND SURVIVAL

Hypophysectomized Rats Treated with Adrenal Cortical Hormone. One of the most striking characteristics of totally hypophysectomized immature animals is the cessation of growth. This has been observed repeatedly, and has a counterpart clinically in pituitary dwarfism. Like-

wise, bilateral adrenalectomy in growing rats produces a disturbance in growth. It might be argued that the fact that completely adrenalectomized young rats cease growing, lose weight, and die, is no proof of a true interference with growth, since they are so acutely ill and have such a relatively short span of life. If, however, these animals are treated with submaintenance doses of the adrenal cortical hormone, they may be kept alive indefinitely, and they exhibit an obvious stunting of growth. The same may be shown in another manner. If young rats are submitted to a bilateral ligation of the adrenal pedicle, similar to the operation first suggested

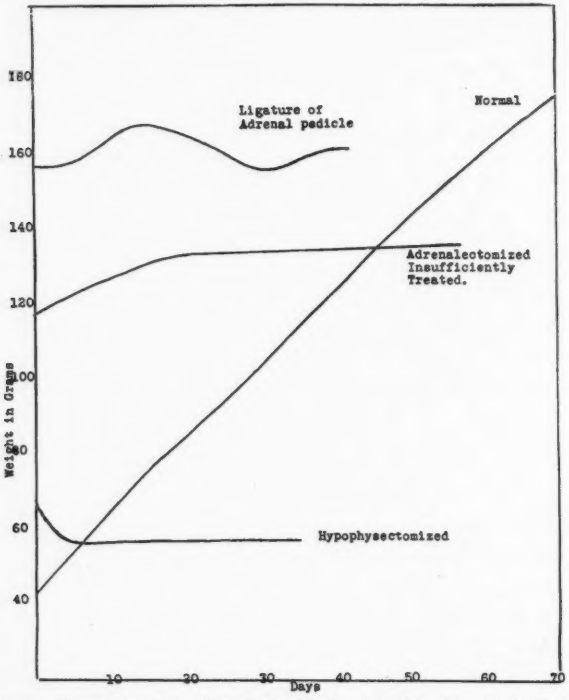

Figure 2. Showing the stunting of growth in adrenal and in pituitary deficiency.

by Boinet in 1895, some of them, in which the adrenal circulation is apparently inadequate, die in a short space of time of acute insufficiency. A second group, in which there is little interference with the adrenal circulation, live and grow normally. A third group remain alive indefinitely in rather good condition, with mild symptoms of adrenal insufficiency. In this group there is a marked retardation of growth. The growth curve of one such animal which did not gain weight significantly for forty-five days is given in Figure 2, together with growth curves of insufficiently-treated adrenalectomized rats, of totally hypophysectomized rats, and of normal rats.

The question immediately arises as to whether this failure of growth in these two different hormonal deficiencies is interrelated. It is well known that hypophysectomized animals resume their normal growth upon administration of homotransplants (5) or potent extracts of the growth hormone (8). Likewise, adrenalectomized rats grow normally if treated adequately with adrenal cortical hormone (Figure 3).

A group of young rats averaging 83 grams in weight were totally hypophysectomized. After their weight curves had become perfectly level

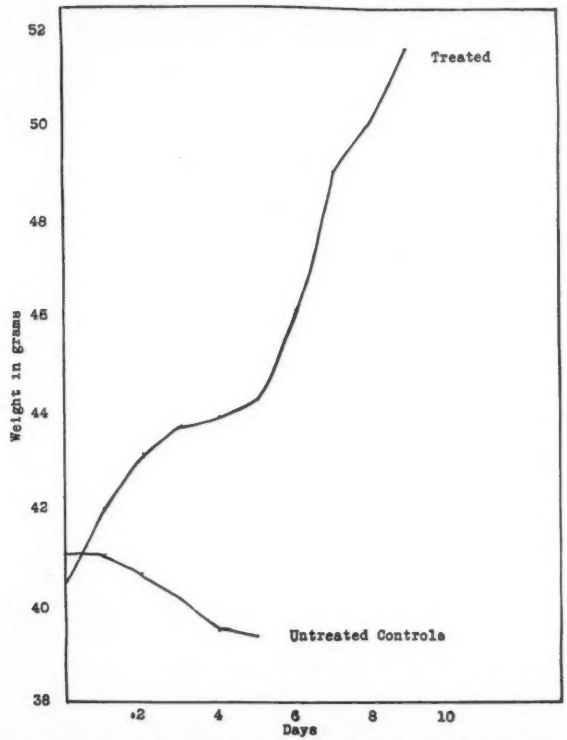

Figure 3. Growth of adrenalectomized rats treated with adrenal cortical hormone. Of the untreated controls, four died on the fourth day, the fifth on the fifth day. All of the five treated animals were alive when treatment was discontinued on the ninth day.

(average twenty-one days after operation) they were divided into two groups. Four of them were treated daily for fourteen days with a potent extract of the adrenal cortical hormone in quantities sufficient (1 cc.) to maintain health and normal growth in completely adrenalectomized animals. As controls, one animal received an inactivated solution of the cortical extract, and two received normal saline, in the same dose and for the same period of time. As will be seen from Figure 4 the growth curves are similar. Certainly, then, the dwarfism of hypophysectomized animals

is not to be explained on a basis of adrenal cortical atrophy or insufficiency. This is in accord with the experiments of Atwell (55, 56) and of Evans and his co-workers (8).

We have observed in our treated animals no change in activity nor betterment of general health as compared with the controls, which is contrary to the claims of Atwell (55). Atwell reported that the temperature of his hypoyhysectomized animals treated with cortin was nearer normal than that of the controls. We observed no such difference, as may be seen in Figure 4. This chart represents morning temperatures taken before injections. We have, in addition, repeatedly taken temperatures hourly following administration of the cortical hormone and have noted no rise. Hartman's extract, which Atwell used, contains appreciable quantities of ascorbic acid (vitamin C) (57). In view of the stimulating

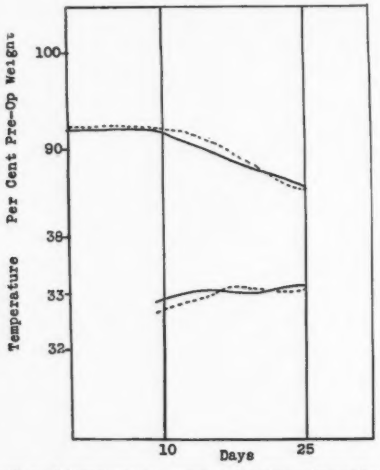

Figure 4. Growth and temperature curves of totally hypophysectomized rats treated with adrenal cortical hormone. Continuous line, treated animals. Dotted line, controls.

effects on metabolism of this substance, its role in eliciting any temperature rise must be considered.

Temperatures were taken at frequent intervals following the injection of normal saline, cortical hormone, and crystalline ascorbic acid, in four totally hypophysectomized rats. Thirty injections were made. The dosage of ascorbic acid varied from one to seven milligrams; cortical hormone was given in dosages of one, two, three, and four rat units; one cubic centimeter of normal saline was used. Following administration of normal saline we obtained the normal variation in temperature. The same type of chart was obtained after injections of the cortical hormone and in no instance did a significant rise follow. Only with ascorbic acid was a significant stimulation of temperature obtained. The results were inconstant. In a few a drop of temperature of 1.5 or 2 degrees Centigrade

occurred, as it did occasionally after injection of the cortical hormone. In a few no change occurred. In half of the experiments, however, a marked and sustained rise in temperature followed, sometimes as great as 2.7 degrees Centigrade. In Figure 5 a typical experiment is recorded.

It would appear most probable, therefore, that the temperature rise in Atwell's experiments may have resulted from vitamin C or some non-specific impurity, rather than from the adrenal cortical hormone itself. The same criticism is to be applied to the results of Baird, Cloney, and Allbright (58), who claimed that adrenal cortical hormone restored to hypophysectomized rats their resistance to cold temperatures.

Hypophysectomized and Unilaterally Adrenalectomized Rats. We have already shown that hypophysectomized rats invariably undergo an atrophy of the adrenal cortex and that if one gland is removed the other adrenal remains atrophic. Assuming this anatomical atrophy to be an index of diminished cortical secretion, it is important to determine the effects of further reducing the available supply of cortical hormone in the

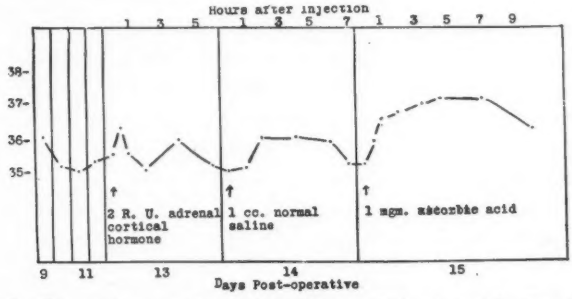

Figure 5. Temperature reaction in hypophysectomized rat to injection of adrenal cortical hormone, normal saline, and ascorbic acid.

hypophysectomized animal. We have studied growth and made observations as to general health and activity in a group of hypophysectomized and unilaterally adrenalectomized rats. The results are charted in Figure 6. It is seen that the growth curve of the five totally hypophysectomized and unilaterally adrenalectomized rats differs in no respect from that of a group of hypophysectomized animals which have both adrenals intact and presumably a larger supply of the adrenal cortical hormone. Likewise, no difference in bodily activity or general health was observed. It is also seen that rats partially hypophysectomized and unilaterally adrenalectomized show a normal growth curve. Their activity was perfectly normal.

When rats are treated with growth hormone, according to Evans and Long (59, 60), excessive growth results. Although Corey and Britton (54) reported that young rats treated with adrenal cortical extract grew faster than their controls, Howard and Grollman (61), using a potent and highly purified hormone, observed no difference in the growth of young

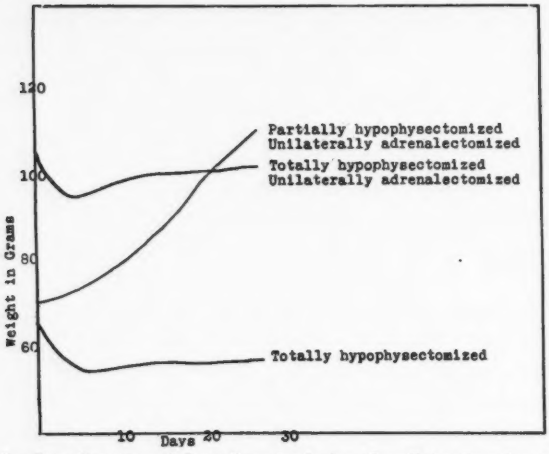

Figure 6. Growth curve of hypophysectomized and unilaterally adrenalectomized rats, and of controls.

rats treated with five times the amount required to maintain completely adrenalectomized rats in good health, as compared with untreated controls.

It seems apparent, then, that the adrenal cortical hormone fails to restore growth, temperature, and normal activity to totally hypophysectomized rats, also that removing one adrenal from hypophysectomized rats fails to influence growth, general health, and activity.

The Effects of Pituitary Homotransplants on Adrenalectomized Rats. Fifty rats were completely adrenalectomized under amytal anesthesia.

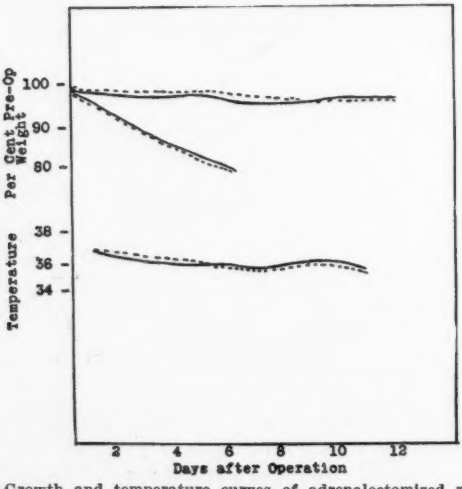

Figure 7. Growth and temperature curves of adrenalectomized rats treated with pituitary transplants, and of controls. Continuous line, treated animals. Dotted line, untreated controls. The growth curves of those animals surviving eight days or more, and of those with shorter survival periods, are plotted separately.

Half of these received daily pituitary homotransplants beginning the day following operation. In Figure 7 are plotted the weight curves of treated and control animals. They are divided into two groups, those surviving eight days or more, and those surviving a shorter period. It is obvious that pituitary transplants did not check the loss in weight nor stimulate growth. Likewise no difference was observed in the temperature charts of the treated animals and the controls. Both groups survived an average of 5.5 days, the maximum survival in both groups being 12 days.

Survival of Hypophysectomized Rats After Bilateral Adrenalectomy. Since hypophysectomized animals survive in reasonably good health with atrophic adrenals and possibly a diminished supply of the cortical hormone, it might be postulated that they would survive total adrenalectomy longer than normal rats accustomed to a possibly greater quantity of the adrenal cortical hormone. Seventeen young rats, which had been hypophysectomized from five to eleven days, were bilaterally adrenalectomized under amytal anesthesia. Although all of them showed stunting of growth, autopsy revealed that six of them contained small remnants of the pituitary gland. These served as controls for the eleven totally hypophysectomized rats. As shown in Table 1 the completely hypophysectomized group survived an average of only two days and nearly fifty per cent of them died within twenty-four hours. In contrast to this the partially hypophysectomized controls survived an average of four days, which is only slightly less than the normal survival period. The adrenals of the first group were atrophic while those of the latter were perfectly normal. The series is too small for any broad conclusions. It is apparent, however, that hypophysectomized animals do not have a prolonged survival period after adrenalectomy, and it may be distinctly shortened.

TABLE 1

SURVIVAL AFTER BILATERAL ADRENALECTOMY IN TOTALLY AND IN PARTIALLY HYPOPHYSECTOMIZED RATS

Days Survival	Totally Hypophysectomized	Incompletely Hypophysectomized
	Per Cent Mortality	Per Cent Mortality
1	45.5	0.
2	27.3	0.
3	18.2	16.6
4	0.	66.6
5	0.	0.
6	9.	16.6

THE REPRODUCTIVE SYSTEM

General Considerations. That both the anterior lobe of the hypophysis and the adrenal cortex are related to the gonads has been suspected from a number of clinical and experimental observations. The influence of the pituitary upon the reproductive system is definite enough. Numerous observers have noted an atrophy of the gonads in hypophysectomized animals, incapacity for mating, and failure of ovulation, spermatogenesis, and

reproduction. We have invariably observed these findings. All of these functions may be restored by replacement therapy (5).

The relation between the adrenals and the gonads, though less definite, is based upon numerous observations. Howard and Grollman (61) have recently reviewed the subject, and have discussed the relation of adrenal neoplasms to certain clinical sex alterations. In addition, some experimental data suggest a relationship between adrenals and gonads. Adrenal insufficiency causes a cessation of estrus (42, 62, 63, 64). Those reports (65, 66, 67) which concluded that estrus was not disturbed by adrenalectomy are obviously invalidated by incompleteness of operation. We have found that adrenalectomized rats treated adequately with the cortical hormone maintain normal estral cycles. The stimulating effects of the adrenal cortical hormone on the reproductive system of young animals claimed by Corey and Britton (54) have been disproved by numerous workers (Cleghorn [68], Howard and Grollman [61], Simpson, Speyer and Korenchevsky [69], etc.).

The Effect of Adrenal Insufficiency on the Weight of the Reproductive Organs. Twenty-seven young female rats and twenty-eight males were bilaterally adrenalectomized under amytal anesthesia. They were treated insufficiently with the cortical hormone, or given no treatment at all. In Tables 2 and 3 are given the weights of the reproductive organs as com-

TABLE 2

THE EFFECT OF ADRENAL INSUFFICIENCY ON THE WEIGHT OF THE FEMALE REPRODUCTIVE ORGANS

Final Weight in Grams	Adrenalectomized				Controls		
	Number Animals	Survival in Days	Average Weight Ovaries in Grams	Average Weight Uterus in Grams	Number Animals	Average Weight Ovaries in Grams	Average Weight Uterus in Grams
30–35	2	3.5	0.017	0.029	1	0.024	0.023
35–40	3	6.7	0.013	0.026	2	0.025	0.023
40–45	9	8.7	0.017	0.027	3	0.024	0.026
45–50	8	10.4	0.016	0.031	2	0.026	0.030
50–55	3	11.3	0.016	0.028	1	0.029	0.034
55–60	1	9.	0.020	0.034	1	0.024	0.036
60–65	1	12.	0.022	0.041	1	0.031	0.041

pared with those of control animals of the same weight. With the females it is apparent that the adrenalectomized animals have undergone a striking ovarian atrophy of an average of about 37 per cent. When the fact is is taken into consideration that these animals lost weight and that, consequently, controls of the same age would be larger animals, the atrophy is more evident. There is little difference in the weights of the uteri of the adrenalectomized animals as compared with the controls. The results with the males are not so clear cut. It appears that, in general, the smaller animals have testes and secondary sex organs slightly smaller than the controls. With the larger rats, the testes, epididymes, and vasa are about the same weight or slightly heavier than in the controls, although the prostate

and seminal vesicles are somewhat smaller. These animals are of an age when there is remarkable growth of the male reproductive organs, and it is likely that comparison with age controls might have shown a decrease in the weight of the adrenalectomized group. These experiments are in accord with the clinical findings of testicular and ovarian atrophy in Addison's disease (44).

TABLE 3

THE EFFECT OF ADRENAL INSUFFICIENCY IN THE WEIGHT OF THE MALE REPRODUCTIVE ORGANS

Final Weight in Grams	Adrenalectomized				Controls		
	Number Animals	Survival in Days	Average Weight Prostate and Seminal Vesicles in Grams	Average Weight Testes, Epididymes and Vasa in Grams	Number Animals	Average Weight Prostate and Seminal Vesicles in Grams	Average Weight Testes, Epididymes and Vasa in Grams
30–35	1	3.	0.026	0.209	1	0.025	0.235
35–40	6	6.	0.018	0.266	6	0.025	0.277
40–45	7	8.3	0.025	0.447	3	0.029	0.302
45–50	7	10.3	0.029	0.483	4	0.039	0.491
50–55	3	11.	0.031	0.514	2	0.041	0.565
55–60	3	12.3	0.042	0.684	2	0.042	0.670
60–65	1	10.	0.030	0.565	1	0.047	0.716

Decreased Sex-Stimulating Power of the Hypophysis in Adrenalectomized Rats. We have previously shown that the pituitary gland undergoes marked alterations in adrenal insufficiency, and that the characteristic change is a striking diminution in the number of normal basophiles. It seemed plausible, then, to explain the gonadal atrophy and disturbance of œstrus by a secondary change in the sex cells of the hypophysis. Martin (64) found that the pituitary gland in adrenalectomized rats shows a diminished ovary-stimulating power. Del Castillo (70), on the contrary, found no decrease in sex-stimulating capacity. We have repeated these experiments.

Healthy normal male rats weighing from 200 to 300 grams were bilaterally adrenalectomized. While in severe insufficiency (average 6.5 days p.o.) they were sacrificed, and their pituitaries transplanted, one a day for three successive days, into young females twenty-eight to thirty days old. Littermate controls were transplanted at the same time with pituitaries from unoperated rats of the same age. Other littermate controls received no treatment. They were all sacrificed on the fifth day. The results are given in Table 4. The untreated controls had uteri and ovaries weighing an average of 0.074 grams, and none of them had an open vagina. Those transplanted with normal pituitaries averaged 0.226 grams, an increase of 205 per cent, and all of them had open vaginae. The weights checked closely. Those rats transplanted with pituitaries from adrenalectomized animals averaged 0.162 grams, an increase of only 119 per cent. Thus they had a 42 per cent decrease in power to hypertrophy uterus and ovaries of immature rats. It is seen that here the weights vary considerably. In some instances the pituitaries have apparently lost practically all of their

Figure 8. Uteri and ovaries from three litter-mate rats, (A) untreated, (B) treated with three pituitary transplants from adrenalectomized rats, and (C) treated with three pituitary transplants from normal rats. One-half natural size.

sex-stimulating activity. In Figure 8 are photographs of the reproductive organs of one litter of rats, illustrating this decrease in gonad-stimulating power. The decrease involves capacity to hypertrophy both uterus and ovaries as we determined by weighing the organs separately in a number of litters. Only 70 per cent of those rats transplanted with hypophyses from adrenalectomized rats underwent an opening of the vagina. These results confirm the work of Martin and contradict that of del Castillo.

TABLE 4

THE EFFECT ON THE FEMALE REPRODUCTIVE TRACT OF PITUITARY TRANSPLANTS FROM ADRENALECTOMIZED RATS

	Number Animals	Body Weight in Grams	Weight of Uterus and Ovaries in Grams	Variation in Weight of Uterus and Ovaries	Condition of Vagina	Increase in Weight of Uterus and Ovaries
Untreated controls.....	10	69.2	0.074		None open	
Normal pituitary transplants.....	10	64.3	0.226	0.201 to 0.259	All open	205%
Pituitary transplants from adrenalectomized rats.....	10	65.6	0.162	0.108 to 0.214	70% open	119%

Pituitary Transplants in Adrenalectomized Rats. Martin (64) reports that he was able to restore estrus to a number of adrenalectomized rats by injections of theelin and of gonad-stimulating hormone. We have carried out experiments on the effect of pituitary transplants on twelve bilaterally adrenalectomized immature females (average weight 84 grams) and on thirteen young males (average weight 95 grams). An equal number of adrenalectomized animals of the same weight served as controls. Transplants were made daily, beginning the day following operation.

The females (Table 5) gave the same response that is elicited by pitu-

TABLE 5

EFFECT OF DAILY PITUITARY TRANSPLANTS ON FEMALE REPRODUCTIVE ORGANS OF ADRENALECTOMIZED RATS

	Number Animals	Pre-operative Body Weight in Grams	Final Body Weight in Grams	Survival in Days	Weight of Uterus and Ovaries in Grams	Variation in Weight Uterus and Ovaries	Condition of Vagina
Untreated controls..	12	83	68.3	5.8	0.066	0.044 to 0.082	None open
Daily transplants...	12	84	70.	5.5	0.163	0.077 to 0.260	58% open

itary implants in unoperated immature females. There was a pronounced increase in the weight of uteri and ovaries. The combined weights averaged 0.066 grams in the untreated controls, and 0.163 in the treated animals. Ovaries weighed separately in eight animals averaged 0.024 grams for the untreated and 0.073 for those receiving transplants. All of those treated which survived six days or longer and one which survived five days underwent opening of the vagina and had normal estral smears. This occurred in 58 per cent of the group. Ovaries from these animals show in the gross numerous bloody follicles.

There is such a marked variation in the weights of the reproductive organs in the males that broad conclusions are hazardous (Table 6). It

TABLE 6

EFFECT OF DAILY PITUITARY TRANSPLANTS ON MALE REPRODUCTIVE ORGANS OF ADRENALECTOMIZED RATS

	Number Animals	Pre-operative Body Weight	Final Body Weight	Survival in Days	Weight Testes, Prostate and Seminal Tract	Variation in Weight Testes, Prostate, Seminal Vesicles	Weight Prostate and Seminal Vesicle
Untreated controls..	13	93.6	82	5.2	1.111	0.26 to 2.545	0.144*
Daily transplants...	13	95.	83	5.5	1.261	0.22 to 2.714	0.254*

*This figure is the average of only 8 of the experimental animals, no separate weighing of the component parts of the reproductive tract having been made in the other 5.

appears, however, that the treated animals have very slightly heavier testes, and distinctly larger seminal vesicles and prostate glands. The difference in the testicular weights is probably not significant. There is a definite hypertrophy of the seminal vesicles and prostate, however, which is confirmed by histological study. Preliminary microscopic studies of the testes seem to indicate that adrenalectomized rats undergo a slight atrophy of the testes. We did not, however, find the marked tubular degeneration which Novak (71) and Freed, Brownfield, and Evans (72) described. We noted no significant difference in the histological picture of the testes of treated and untreated animals. Freed, Brownfield, and Evans failed to prevent atrophic changes with injections of urine of pregnancy hormone. We are at present investigating more fully the changes in the male reproductive tract in adrenal insufficiency.

Adrenal Cortical Hormone Therapy in Hypophysectomized Rats. Four totally hypophysectomized rats, two males, two females, were treated for two weeks with adrenal cortical hormone in sufficient doses to maintain life and health in adrenalectomized rats. At autopsy no gross nor microscopic evidence of any influence whatsoever upon the reproductive organs was apparent. Ovaries, uteri, and testes showed the same picture of marked atrophy that characterized these organs in control animals which received no cortical hormone. This is confirmatory of the work of Atwell (55) and in contradiction to that of Migliavacca (73), who found luteiniza-

tion of the ovaries of pituitary irradiated animals treated with cortical extract.

SUMMARY

The experimental and clinical literature concerning anatomical changes in the adrenal glands in hyper-pituitarism and hypo-pituitarism has been reviewed. The initial alterations in the adrenal cortex in hypophysectomized rats was studied in 18 animals sacrificed at varying periods after operation. The failure of compensatory hypertrophy of the adrenals in hypophysectomized rats was confirmed (6 animals). The pituitary findings in one dog kept in chronic adrenal insufficiency for a long period was presented, together with a discussion of the pituitary pathology of Addison's disease and experimental insufficiency described in the literature. Failure of growth was demonstrated in hypophysectomized rats and in rats with chronic adrenal insufficiency. The restoration of growth in adrenalectomized rats (5) treated with adrenal cortical hormone was confirmed. Temperature, weight, activity, and gonadal structure were studied in hypophysectomized rats (4) treated with the cortical hormone, and in rats (3) receiving control injections. Study was made of the temperature reaction following thirty injections of normal saline, ascorbic acid, and the cortical hormone, in four hypophysectomized rats. The weight changes in hypophysectomized rats (5) deprived of one adrenal gland were recorded. Temperature, weight, and general activity in 25 adrenalectomized rats receiving daily pituitary transplants were compared with an equal number of untreated adrenalectomized controls. The survival after adrenalectomy was studied in totally (11) and in incompletely (6) hypophysectomized rats. Weights of gonads and secondary sex organs in young adrenalectomized animals (27 females, 28 males) were compared with normal controls. The sex-stimulating power of pituitaries from 30 adrenalectomized rats were studied by transplants into ten immature females, litter-mates serving as controls. The effect of daily pituitary transplants on the reproductive organs of 12 adrenalectomized females and 13 males was ascertained by comparison with an equal number of untreated controls. From these experiments, the following conclusions may be drawn.

Both clinically and experimentally, severe pituitary deficiency causes a striking atrophy of the adrenal cortex, which may be restored to normal in animals by substitution therapy. Hyperpituitarism conversely results in a hyperplasia of the adrenal cortex. Hypophysectomy destroys the capacity of the adrenal gland to undergo compensatory hypertrophy if one gland is removed. Likewise, adrenal insufficiency results in anatomical changes in the hypophysis, the most characteristic of which is a diminution in the number of the normal basophilic cells.

Both pituitary and adrenal deprivation cause a stunting of growth, inactivity, and lowered body temperature. Growth cannot be restored to hypophysectomized animals, activity increased, nor temperature raised by potent extracts of the adrenal cortical hormone. In addition, hypophysec-

tomized animals may be submitted to unilateral adrenalectomy without affecting weight, general activity, or health. Weight loss cannot be checked in adrenalectomized rats, nor growth stimulated by transplants of the pituitary gland, nor is the subnormal temperature raised, general health improved, nor survival prolonged. The survival period after bilateral adrenalectomy is shortened by a preliminary hypophysectomy.

In both hypophysectomized and adrenalectomized animals there is atrophy of the reproductive system with marked alteration in sex activity. The dysfunction and atrophy of the reproductive organs of hypophysectomized animals is not a secondary manifestation of the lack of adrenal cortical hormone, for administration of the latter fails to repair the observed changes in the reproductive tract and to restore sex functions. The sex changes in adrenal insufficiency are, on the other hand, probably secondarily dependent upon degenerative alterations in the basophilic cells of the anterior lobe of the pituitary gland. The hypophyses of adrenalectomized rats show a decrease in gonad-stimulating power. Pituitary transplants induce estrus in adrenalectomized female rats, and not only prevent ovarian atrophy, but even stimulate excessive genital growth and premature sexual maturity. Pituitary implants induce premature sexual maturity in adrenalectomized immature female rats.

We wish to make acknowledgment to Dr. Arthur Grollman for providing us with adrenal cortical hormone and for numerous valuable suggestions.

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HYPOTHYROIDISM INDUCED BY COMPLETE REMOVAL OF THE NORMAL THYROID GLAND IN THE TREATMENT OF CHRONIC HEART DISEASE*‡

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During the past 18 months we have treated 75 patients with heart disease by inducing hypothyroidism through complete removal of the normal thyroid gland (1) (2) (3) (4). This procedure has been employed to decrease the demands on the overburdened heart by means of the lowered metabolic rate of hypothyroidism. The treatment of one disease by establishing another is not a new therapeutic concept. The value of such a method of treatment must be determined by weighing the degree of improvement in the original disease against the disadvantages which result from the artificially induced condition. Studies of the beneficial effects of total ablation of the thyroid on heart disease have been reported elsewhere (1) (2) (3) (4). The purpose of this communication is to summarize our clinical and laboratory studies of the development, characteristics, and control of the myxedematous state following complete thyroidectomy in these patients with various types of congestive failure and angina pectoris. This opportunity for studying hypothyroidism was unique, since the observations made on these patients with hypothyroidism could be evaluated at frequent postoperative intervals in reference to the findings in the same patients before total thyroidectomy.

METHOD OF INDUCING PERSISTENT HYPOTHYROIDISM

In order to be sure that hypothyroidism will persist, it has been found necessary to perform complete ablation of the normal thyroid gland. In the first two patients with chronic heart disease but with no evidence of thyroid toxicity who were operated in our clinic, approximately nine-tenths of the normal thyroid gland was removed. Although temporary significant decreases in the basal metabolic rate were effected by this procedure, clinical evidences of hypothyroidism did not develop, and the basal metabolic rates returned to approximately the preoperative levels by the end of the second postoperative month (1). Other investigators have also performed subtotal removal of the normal thyroid gland in patients with no hyperthyroidism without producing manifestations of hypothyroidism (5) (6) (7) (8) (9). That residual thyroid tissue does resume the function of the normal gland

*Address delivered before the American Society for the Study of Goiter, June 7, 1934, Cleveland, Ohio.

‡The studies reported here represent the combined efforts of our associates.

†The expense of these investigations was defrayed in part by the William W. Wellington Memorial Research Fund of Harvard University.

is further evidenced by the experimental work of Halsted (10) and by the infrequency of development of permanent myxedema following subtotal thyroidectomy in patients with thyroid disease (11). We have also found in six patients that massive roentgen irradiation applied to the normal thyroid gland is ineffective in producing a persistent lowering of the basal metabolic rate (12). These observations have led us to believe that nothing short of complete removal of the thyroid gland can, at the present time, insure the development of persistent hypothyroidism. In the patients who form the basis of this report, total thyroidectomy was performed,* and a hypothyroid state has developed and persisted in every instance.

THE DEVELOPMENT OF THE HYPOTHYROID STATE

We have followed the development of hypothyroidism after total thyroidectomy by studying the lowering in the basal metabolic rate, the appearance of clinical signs and symptoms of myxedema, and the increase in the serum cholesterol concentration. These observations have been made simultaneously at frequent intervals during the first few postoperative months.

Changes in Basal Metabolic Rate. Studies of the basal metabolic rate at weekly intervals following total thyroidectomy revealed a consistent and gradual decrease. By the end of the first postoperative week an appreciable fall in basal metabolism was usually observed. The metabolic rate reached its lowest values at some time between the end of the third week and the second month after operation. During the first month after operation the average rate of decrease of the basal metabolic rate is practically the same as that observed when thyroid medication is suddenly omitted in patients with spontaneous myxedema in whom the basal metabolic rate had been maintained at the standard normal level by thyroid medication (13) (Fig. 1). The lowest levels of metabolic rate observed in our patients were usually between minus 25 and minus 35 per cent. In five of our patients levels of metabolism as low as minus 41 to minus 47 per cent were observed after total thyroidectomy. Although such levels of metabolism could not be allowed to persist because of untoward symptoms of myxedema, it is believed that they represent the approximate metabolic levels of completely thyroprival individuals. This level of approximately minus 45 per cent accords with the lowest levels observed in spontaneous myxedema and is in agreement with the concept of Means (14) that the normal thyroid activity controls about 40 to 45 per cent of the caloric requirements of the human subject.

During the second month after total thyroidectomy the basal metabolic rate usually did not show as striking a further decrease as is observed in patients with marked spontaneous myxedema during the second month after omission of thyroid medication (Fig. 1). Some of the patients whose basal metabolic rates have persisted at levels of minus 25 to minus 30 per cent have not developed untoward symptoms of myxedema, although most pa-

*These operations were performed by Dr. David D. Berlin or by Dr. Charles G. Mixter.

tients have required small doses of thyroid to remain comfortable at such levels. The fact that occasionally marked myxedema does not develop leads us to believe that even after as extensive a thyroidectomy as is performed in our cases, minute amounts of functioning thyroid tissue may at times remain in situ or in aberrant positions. Those patients who may thus have minimal thyroid activity are particularly fortunate, in that marked signs and symptoms of myxedema do not develop, and yet the basal metabolic rate persists at levels of minus 25 to minus 30 per cent. At these levels of metabolism the basal velocity of blood flow is slowed and the basal minute volume output of the heart is diminished, in accord with our earlier findings (15) and with those of others (16) in studies of patients with hypothyroidism.

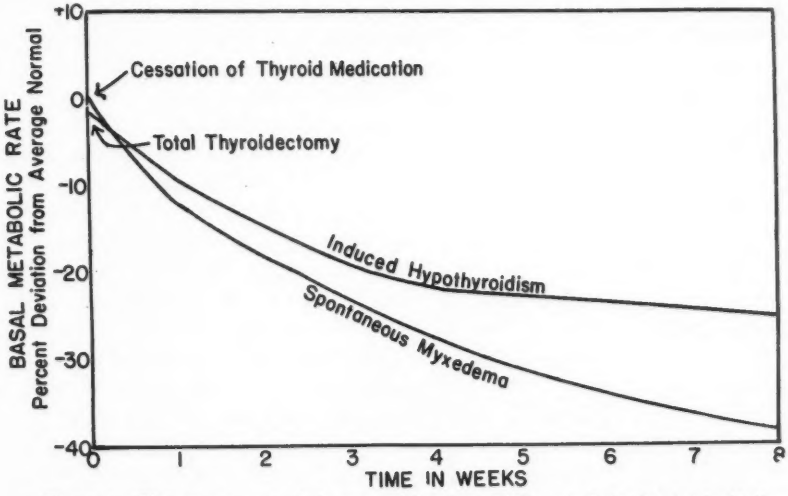

Figure 1. The average rate of decrease of basal metabolic rate following total ablation of the normal thyroid gland as compared with average decrease following omission of thyroid therapy in spontaneous myxedema patients, whose basal metabolic rate had been brought to the standard normal level by thyroid medication. The curve for the spontaneous myxedema group is from Means and Lerman (13); the curve following total thyroidectomy is based on an analysis of our first fifty consecutive thyroidectomized patients.

Since, following total thyroidectomy, the untoward symptoms of myxedema are almost always manifest when the basal metabolic rate decreases below minus 30 per cent, the net reduction in basal metabolism which can be obtained by the operation depends largely upon the preoperative basal metabolic level. Thus, if the preoperative metabolic level is minus 20 per cent, the patient can experience a further drop of only 10 per cent after total thyroidectomy before untoward symptoms intervene. Inasmuch as the clinical improvement to be gained from total thyroidectomy depends upon the lowering of the metabolic rate and accompanying reduction in cardiac work, patients in whom only a moderate lowering in basal metabolic rate can be induced show less striking improvement. In our experience we have observed several patients with angina pectoris and several entirely

normal individuals who have had basal metabolic rates between minus 15 and minus 25 per cent without, however, the slightest clinical evidence of hypothyroidism. Because of the above considerations, we are disinclined to operate on patients whose basal metabolic rates are below minus 15 per cent (4).

Clinical Signs and Symptoms of Hypothyroidism. The first definite clinical signs and symptoms of hypothyroidism generally appeared between the first and second months after operation. Many patients at this time noted coldness of the extremities, dryness of the skin, and absence of sweating. Slowing in the rate of hair growth, slight pallor and mild myxedematous facies were also observed early. During the second to sixth postoperative months approximately 90 per cent of our patients developed the further symptoms of myxedema: puffiness of the face or extremities, irritability, fatigue and stiffness of the extremities, and drowsiness; occasionally tinnitus, numbness of the fingers, or swelling of the tongue were present. The occurrence of these "untoward" symptoms of myxedema usually necessitated small amounts of thyroid medication. The onset of untoward symptoms was often sudden, but usually did not occur for a period of weeks or even months after the basal metabolic rate had remained at low levels. Those cases who showed a drop of metabolism to levels of minus 35 per cent or lower developed untoward symptoms of myxedema within a few weeks after the onset of such low levels. That there is a rather critical level of metabolism below which the untoward symptoms of myxedema develop is not only evidenced by our results but also by those of Thompson (17), who has shown that following treatment for exophthalmic goiter, metabolic levels of minus 20 to minus 25 per cent may persist for a considerable period without the development of clinical signs and symptoms of myxedema. Thompson observed two patients who did not develop myxedema, although their metabolism fell temporarily to levels as low as minus 38 and minus 44 per cent. In these patients the low levels of metabolism persisted only for two or three weeks. The absence of development of clinical symptoms of myxdema in such cases may be explained by the above observations that a few weeks must usually elapse between the development of a low basal metabolic rate and clinical myxedema.

The most frequent manifestation of advanced myxedema first noted in our patients after total thyroidectomy was mild, intermittent subcutaneous swelling, most obvious usually in the eyelids, although generalized puffiness of the face or transient swelling of the hands or lower legs was frequently noted simultaneously. Several of our patients first complained of fatigue in the muscles of the extremities on exertion. If the fatigue was mild and thyroid medication was not instituted immediately, it gradually disappeared in a few patients spontaneously, while in others it progressed to the point where thyroid medication was necessitated. Drowsiness appeared early in only a few patients; occasionally the first complaint was irritability.

Thyroid medication could be so administered as to control all of the

untoward signs and symptoms of myxedema and yet allow the basal metabolic rate to remain at levels of minus 20 to minus 30 per cent. At this level of metabolism the patients usually still note dryness of the skin, sensitivity to cold, lack of perspiration, slowing in the rate of hair growth and, occasionally, easy fatigability and "slowing down." Although speech is somewhat slowed, psychological tests have shown that mental acuity is not impaired in these patients whose myxedematous state is controlled. Some of our patients state that they are able to think more clearly than before operation, due probably to the fact that they compare their postoperative state with the torpor of advanced circulatory failure. Many of our patients who do not have untoward symptoms of myxedema, either because they are controlled with small doses of thyroid or because they never developed these symptoms, show mild myxedematous facies, perhaps recognizable because we have been able to observe the same patients a few months previous to the development of hypothyroidism.

Changes in Serum Cholesterol. Following total thyroidectomy a gradual, consistent increase in serum cholesterol concentration occurred which was accompanied during the first one or two months by a decrease in the basal metabolic rate (17). An increase in the serum cholesterol, as well as the decrease in the metabolic rate, has been observed as early as the end of the first postoperative week. These are the earliest laboratory changes indicative of the development of hypothyroidism which we have observed. It is interesting to note that Curtis and Barron, who have studied iodine metabolism after total thyroidectomy (19), observed definite decreases in the blood iodine and increases in urinary iodine within the first few days following total thyroidectomy. We have observed, in a large group of patients, that although the basal metabolic rate reaches its approximately lowest level within the first two postoperative months the serum cholesterol continues to increase during the following few months. Whereas, the untoward symptoms of myxedema might not develop until the basal metabolic rate had remained at a low level for some time, untoward symptoms were immediately manifest, almost without exception, when the serum cholesterol increased above 300 mg. per cent (18) (20).

In some cases the height of the serum cholesterol concentration accorded with the clinical findings more exactly than did the basal metabolic rate. Thus, in a few of our patients who, after total thyroidectomy, showed marked clinical evidences of myxedema, the basal metabolic rate was not decreased below minus 20 per cent, possibly due to the fact that the patients were unable to relax sufficiently to obtain the truly basal state. Such patients, however, usually had serum cholesterol values of 300 mg. per cent or higher. Thyroid in small doses ($\frac{1}{10}$ to $\frac{1}{2}$ grains daily, Armour's) caused a reduction in serum cholesterol.

There seems to be a rather general belief that myxedema and hypercholesterolemia predispose to arteriosclerosis. There is little evidence from observations in man (21), however, to support this belief. In six of our

patients who have had hypothyroidism and associated hypercholesterolemia for a period of over a year, roentgenographical studies of the blood vessels show no apparent increased density.

The Effectiveness of Small Doses of Thyroid in Controlling the Hypothyroid Level. Thyroid treatment in our patients has been symptomatic, a direct attempt being made to control the untoward symptoms of myxedema and at the same time to maintain the basal metabolic rate at the lowest practicable level. This method of thyroid therapy with emphasis on dissipating the untoward symptoms rather than bringing the metabolic rate to the standard normal level is to be contrasted with the procedure employed in treating patients with spontaneous myxedema.

Thyroid medication to control the untoward symptoms of myxedema is usually first prescribed between the second and sixth postoperative months. If patients do not develop untoward symptoms of myxedema by the end of this period, there is little likelihood that thyroid medication will ever be required; all but five patients of our series who are more than six months postoperative require thyroid. Amounts of thyroid varying between $\frac{1}{10}$ and $\frac{1}{2}$ grains daily (Armour's) have been found sufficient to free these patients with induced myxedema from distressing symptoms. On these amounts of thyroid the basal metabolic rates have remained at levels between minus 25 and minus 30 per cent in most cases. On rare occasions we have noted that even $\frac{1}{4}$ grain of thyroid extract daily (Armour's) may increase the basal metabolic rate to the standard normal level. Such experiences indicate the importance of proceeding with great caution in the administration of thyroid; whether a given patient will require $\frac{1}{10}$ or $\frac{1}{2}$ grain of thyroid daily to free him from the distressing symptoms of myxedema must be determined by trial. The most frequent optimal dose of thyroid for our patients has been $\frac{1}{4}$ grain daily.

The small dosage of thyroid which is sufficient to maintain a patient free from the untoward symptoms of myxedema is markedly less than the $1\frac{1}{2}$ to 3 grains daily of thyroid (Armour's) which is required to maintain the metabolism of myxedematous patients at the standard normal level (17). This principle of minimal thyroid dosage to control the distressing symptoms of myxedema and still allow the metabolism to remain at levels of minus 25 to minus 30 per cent may likewise be applied in the treatment of patients with spontaneous myxedema who develop anginal attacks or congestive heart failure when the basal metabolic rate is brought to normal by thyroid medication.

DISCUSSION

We have outlined above the development, characteristics and control of the hypothyroid state induced by total ablation of the normal thyroid gland, with special reference to the signs and symptoms of hypothyroidism, the basal metabolic rate and the serum cholesterol. The method of thyroid medication has been described whereby the hypothyroid level, after total

thyroidectomy, may be controlled so that patients with heart disease may be free from the distressing symptoms of myxedema and yet gain the benefits afforded by reduction in the work of the heart. In addition to the manifestations of hypothyroidism reported above which are present at a basal metabolic level of minus 25 to minus 30 per cent, we have also observed the development of a mild anemia and a lowering in the free hydrochloric acid in the gastric secretion. No clinical symptoms have been associated with these changes. At this controlled level of metabolism we have also noted changes in electrocardiographic tracings and heart size characteristic of mild hypothyroidism. These changes were not accompanied by a decreased functional myocardial capacity; on the contrary, these patients with chronic heart disease have shown improvement in the face of such changes. Kidney function and carbohydrate tolerance are not diminished in these patients.

In brief, hypothyroidism can be induced by total ablation of the normal thyroid gland, and the level of the hypothyroid state thus induced can be controlled, so that the patients remain comfortable and yet gain the benefits afforded by reduction in cardiac work. Under these conditions of reduced metabolism the relief which has been afforded many patients with chronic heart disease has been definite. The symptoms which characterize the level of hypothyroidism maintained in these patients after operation are slight and, in the opinion of our patients, insignificant in comparison with the benefits derived.

SUMMARY AND CONCLUSIONS

1. Clinical and laboratory studies of the development, characteristics, and control of the myxedematous state following complete thyroidectomy in 75 patients with various types of congestive failure and angina pectoris are described.

2. The necessity of removing every vestige of the normal thyroid in order to insure the development of persistent hypothyroidism is pointed out.

3. After complete thyroidectomy, the basal metabolic rate usually showed an appreciable lowering by the end of the first postoperative week and reached its lowest values at some time between the end of the third and ninth week after operation.

4. At the reduced levels of metabolism after operation, cardiac work is lessened according to measurements of the velocity of blood flow and minute volume output of the heart.

5. The first definite clinical signs and symptoms of hypothyroidism generally appeared between the first and second months after operation and usually did not occur until after the basal metabolic rate had remained low for weeks or even months.

6. Following total thyroidectomy a gradual, consistent increase in serum cholesterol concentration occurred which was accompanied during the first one or two months by a decrease in the basal metabolic rate. Where-

as the basal metabolic rate reached its approximately lowest level within the first two postoperative months, the serum cholesterol concentration continued to increase during the following few months.

7. Although the discomforting symptoms of myxedema frequently did not develop until the basal metabolic rate had remained at a low level for some time, untoward symptoms were immediately manifest, almost without exception, when the serum cholesterol increased above 300 mg. per cent.

8. In some cases the height of the serum cholesterol concentration accorded with the clinical findings more exactly than did the basal metabolic rate.

9. Thyroid treatment in our patients has been symptomatic, a direct attempt being made to control the untoward symptoms of myxedema and at the same time to maintain the basal metabolic rate at the lowest practicable level. Amounts of thyroid varying between $\frac{1}{10}$ and $\frac{1}{2}$ grains daily (Armour's) have been found sufficient to free these patients with induced myxedema from distressing symptoms. One-quarter grain daily was the usual dose.

10. The principle of minimal thyroid dosage to control the distressing symptoms of myxedema and still allow the metabolism to remain at levels of minus 25 to 30 per cent may likewise be applied in the treatment of patients with spontaneous myxedema who develop anginal attacks or congestive heart failure when the basal metabolic rate is brought to normal by thyroid medication.

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SIMULATION OF PROGRESSIVE MUSCULAR ATROPHY BY EXOPHTHALMIC GOITER

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That myasthenia, sometimes severe, may be a part of the picture in exophthalmic goiter, has long been known. That marked muscular atrophy may also occur is less widely recognized.

For some years we have been interested in localized muscle atrophies seen in certain of our thyrotoxic patients, usually in the temporal or thenar regions, but it was not until two years ago that we encountered a picture simulating that of progressive muscular atrophy, subsequently proved to be due to exophthalmic goiter.

The patient in question, a Polander of 48, entered the Neurological Service of the Massachusetts General Hospital (Hospital Number 321056) on May 3, 1932, when a preliminary diagnosis was made by one of us (J. B. A.) of "muscular atrophy associated with chronic systemic disease."

The story was that of progressive weakness and wasting, together with marked muscular twitchings, all of which had begun after a "cold" seven weeks before. There had been a coincident weight loss of 24 pounds. There had been also slight dyspnoea, but this was less prominent in the patient's mind than the weakness, especially in his legs. His appetite had been fair; his bowels regular. There had been no increased sweating or diarrhoea. The past and family histories were non-contributory.

Physical examination showed him to be very emaciated, with marked atrophy of the muscles of his face and temples. Indeed, all the muscles of the body showed definite wasting, with generalized fibrillary twitching. There was well-marked loss of power and tone of muscles, but no sensory changes or abnormal reflexes.

His eyes were somewhat prominent and staring, and showed a lid lag. There was some tremor of the extended fingers and very slight fullness of the thyroid with faint bruit. There was moderate tachycardia. These findings led to a determination of the basal metabolic rate, which to our surprise turned out to be plus 58 per cent.

The other physical and laboratory findings, including the spinal fluid, were not remarkable.

The patient was given iodine in the customary dosage for toxic goiter and, as shown in Figure 1, made a response characteristic of that condition.

Believing that he had two diseases, for one of which only is there a successful treatment, we had a subtotal thyroidectomy performed on May 23, 1932. He made an uneventful recovery and we have followed him carefully ever since.

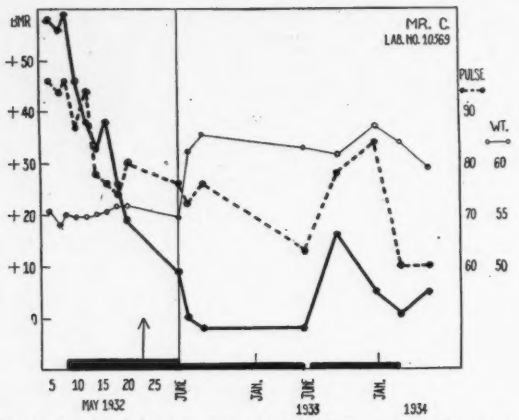

Figure 1. Chart showing behavior of basal metabolism, pulse and weight. Iodine administration is shown in heavy black at bottom of chart, operation by the arrow. There is a prompt response to iodine in the beginning, and nearly two years after operation the metabolism is normal, off iodine.

The remarkable thing about the follow-up is that the operation seemingly cured, not only his exophthalmic goiter, but his muscular atrophy as well. His muscles filled out with surprising promptness, and two weeks after operation muscular twitching, which had lessened under iodine, had almost ceased. Muscular strength returned along with the disappearance of the thyrotoxic symptoms.

DISCUSSION

The effect of thyroidectomy in this case forced us to conclude that we were not dealing with two coincident diseases, but that the whole picture was the result of thyrotoxicosis. The etiological factor responsible for the thyroid overactivity, we now believe, was responsible for the muscular atrophy, which in this patient was so conspicuous as to dominate the clinical picture.

These morbid changes in the muscles have been discussed by Askanazy (1) in an exhaustive study of four patients with hyperthyroidism, who came to autopsy. He found a diffuse process in all striated muscles, including the extrinsic muscles of the eyeball, consisting of degenerative atrophy of muscle cells, fatty infiltration, loss of striation and uniform appearance, vacuolization and proliferation, and degeneration of nuclei. Cardiac and smooth muscle, he found, was not involved in this process. Not all muscle groups were equally involved, nor were the same muscles involved in different patients. This fits with our own observation on temporal muscle atrophy mentioned at the beginning of this paper. It may be the temporal muscles that chiefly suffer in one case, the thenar or interossei in another, or occasionally all great muscle groups, as in the present case. One is tempted to believe that even exophthalmos may be attributed to this same general process, the muscular balance of the eyeball being upset by the degenerative lesions of the recti.

The precise clinical classification of the muscle picture in the present case is difficult. The generalized atrophy and fibrillary twitchings were more marked and more widespread than one usually sees in classic progressive muscular atrophy, in which the wasting usually begins in the hands and spreads slowly upward, ending in bulbar palsy. In this man we had a rapidly progressive, universal muscle atrophy, with the exception of the tongue and muscles of deglutition, which were unaffected. Also the reaction of his affected muscles to Faradism was prompt, unlike the electrical excitability of muscles in classic progressive muscular atrophy. Although the spinal fluid findings in progressive muscular atrophy are conceded to be normal, we might reasonably expect, in such an acute case as this one, if due to spinal cord pathology, some evidence in the spinal fluid; but the fluid was quite negative—3 lymphocytes and 23 milligrams per cent protein, giving evidence against an inflammatory or metabolic lesion of the spinal cord.

Progressive muscular dystrophies, supposedly disorders of muscle, present a variety of clinical syndromes, but for the most part are more slowly progressive than the progressive muscular atrophies of neurologic origin. Usually they show a selective quality, the axial muscle groups being earliest affected. The age of onset is typically much younger than in our patient. For neurological diagnosis, therefore, we are forced to admit that our patient does not fit clinically recognizable entities and we must fall back on descriptive terms: a rapidly progressive, generalized progressive muscular atrophy with generalized twitchings, associated with obvious thyrotoxicosis.

The case becomes of interest at the present time, particularly in view of the recent work of Shorr, Richardson and Wolff (2). These investigators, in studying the nature of the muscular weakness of Graves' disease, found certain biochemical similarities to progressive muscular dystrophy. Creatinuria is common to both conditions and in both, according to their observations, the ability to retain ingested creatine (presumably as phosphocreatin) is markedly diminished. They concluded that the processes maintaining the integrity of the phosphocreatin mechanism in thyrotoxicosis are overtaxed in the presence of persistently high metabolism and that "the muscular weakness of Graves' disease is the result of a reparable impairment of the phosphocreatin mechanism, and is of the nature of an acute muscular dystrophy, similar in many respects to the disturbance in progressive muscular dystrophy." We have no observations of creatine output in our case, but its clinical features seem to exemplify so completely the contentions of Shorr, Richardson and Wolff as to merit record.

We have searched the literature for case reports of similar type. Sattler, who reviewed the literature up to 1908, refers to several case reports of muscular atrophy associated with hyperthyroidism. However, in most instances, the atrophy was either localized or associated with neurologic changes. Only two or perhaps three of the patients referred to had generalized atrophy of the type reported here. Since Sattler's

review, another case has been reported by Sterling (4). His patient had typical Graves' disease with generalized muscle atrophy, but no fibrillary twitchings. Unfortunately, no mention is made in the report of what happened to the muscles when the thyrotoxicosis was ameliorated.

SUMMARY

The case is reported of a man of 48 who initially presented simultaneously the pictures of progressive muscular atrophy and exophthalmic goiter.

Following a sub-total thyroidectomy conditions normalized as regards both manifestations. The wasted muscles filled out and muscular strength returned.

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A NEW PROCEDURE FOR THE DEMONSTRATION OF ESTRIN IN THE BLOOD OF WOMEN*

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The pioneer work of Frank and Goldberger, Loewe, Siebke, Mazer, and others demonstrating the presence of the ovarian follicular hormone in the blood of women at different stages of the menstrual cycle has directed attention to the possibilities of adapting such procedures to the study of abnormal menstrual conditions. The relatively large amounts of blood required, the necessary and laborious extraction of the blood, and the yield of insufficient material to inject more than one test animal are, however, disadvantages of the present technique which call for a more efficient and less complicated procedure. The purpose of this report is to present the results of my attempt to develop a simpler method for the determination of the presence of estrin† in the blood, which may be adapted to quantitative as well as qualitative studies.

The Allen-Doisy test for estrin is based on the stimulation of the atrophied vaginal mucosa of mice or rats to develop into a cornified squamous epithelium, readily demonstrable by the use of smears. The procedure employed in this study is dependent on the histologic demonstration of certain changes in the vaginal mucosa of recently spayed mice which precede cornification, the most important of which is the formation of tall, columnar cells secreting mucus (mucification). This transformation has been long recognized, and was formerly thought to be a specific effect of a corpus luteum hormone. It was found during pregnancy and "pseudopregnancy" in the rat (Long and Evans [1]); it occurs in the vagina of immature mice used for the Aschheim-Zondek test when the ovaries of the test animal contain only luteinized structures (Wiesner [2], Fluhmann [3]), and also after the administration of "luteinizing" extracts of the placenta or the anterior hypophysis (Wiesner [2], Evans and Simpson [4]); and it has been produced experimentally by the injection of extracts of the corpus luteum in immature mice by Wiesner and Patel (5), in rats by Hisaw, et al. (6), in spayed mice by Clauberg (7), and in guinea-pigs and mice by Harris and Newman (8). Courrier (9) produced such changes in immature mice by the injection of follicular fluid, while in 1930 it was shown by Fluhmann (10) that mucification of the vagina of the adult

*Supported in part by a grant from the Rockefeller Fluid Research Fund of Stanford University School of Medicine. The test animals were kindly donated by Dr. C. H. Danforth of the Department of Anatomy.

†The term "estrin" is used throughout this study as a generic name for estrogenic hormones occurring in the blood of women. It is now known that several compounds have this property, and it is by no means certain that "theelin" is the only one found in the circulation of normal individuals.

spayed mouse could be readily induced by the administration of blood serum from both men and women and that it could not be considered a reliable test for the presence of progestin. The work of Robson (11), Robson and Wiesner (12), and Meyer and Allen (13, 14) has since demonstrated conclusively that mucification is an effect of estrin, and that the production of this change by corpus luteum extracts is due to the presence of small amounts of estrin in these preparations.

TECHNIQUE

The blood is obtained by venapuncture and immediately placed in a test-tube for transmission to the laboratory. From 25 to 40 cc. are taken each time, according to the amount required. The clear serum is secured by centrifugalization, and the cells are discarded. If it is kept sterile, the serum may be left in the ice-box for days and even weeks without losing its potency.

The animals used are adult female mice, which have been spayed 6 to 7 days prior to the day the test is begun. This is important, for if the period of castration is shorter the vaginal mucosa may show unusual changes difficult of interpretation at the end of the test, while if it is longer the mice are not as sensitive to the action of estrin. It may be possible to "sensitize" old castrates by the administration of a cornifying dose of estrin some days before they are used, but this method has not been resorted to. The usual procedure has been to do a bilateral oophorectomy on the mice on a Tuesday and to begin all tests on the same day of the following week.

A total of 4.5 cc. of blood-serum is given to each mouse, and the test is completed in 72 hours.* The serum is administered subcutaneously in the back, and the site of each injection is varied as much as possible to facilitate absorption. Three injections of 0.5 cc. are given daily, at 8:00 a.m., noon, and 5:00 p.m., for three consecutive days. On the fourth morning the animal is sacrificed and the vagina is carefully dissected free. This is a simple procedure and is accomplished by making a long incision in the abdominal wall and separating the symphysis pubis. As many as 20 to 30 autopsies may be done in a half hour. The vagina is fixed in formalin, mounted in paraffin, and transverse sections are made at different levels and stained with hematoxylin-eosin.

In the preliminary report of this work (Fluhmann [15]) no differentiation was made of the intensity of the changes elicited in the mouse vagina, but this has been very unsatisfactory. It has now been found possible to recognize six reactions, as follows:

*An attempt is now being made to shorten this period to 48 hours, and it has already been shown that mucification may be readily induced in that time. On the basis of some unpublished observations it seems that the intensity of estrin effects does not depend altogether on the total amount of hormone injected but also on the concentration maintained in the test animal. It thus may be possible to intensify the reactions elicited by giving the test animal 6 injections of 0.75 cc. in two days.

Reaction 0. Atrophy of the vagina. Mucosa shows two layers of low cuboidal epithelium. Occasional leucocyte. (Figure 1.)

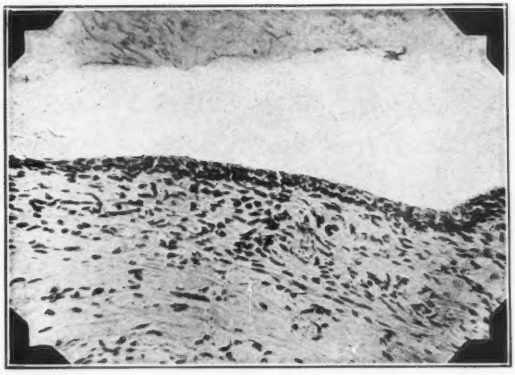

Figure 1. Negative reaction. Vaginal wall of a mouse spayed 9 days before.

Reaction 1. Vaginal mucosa shows two layers, a basal of low cuboidal epithelium and a superficial of tall columnar cells. A few leucocytes. (Figure 2.)

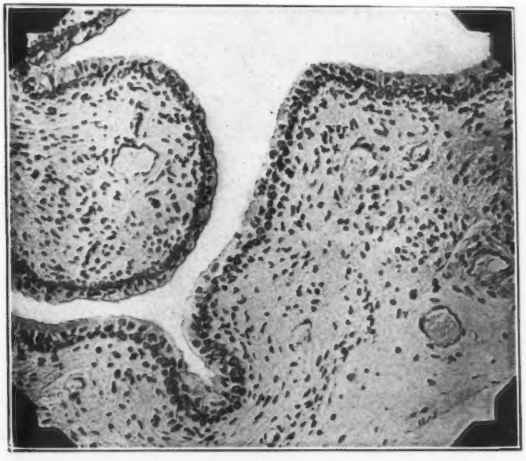

Figure 2. Early development of mucified cells in the vaginal wall of a spayed mouse.

Reaction 2. The superficial cells are high, begin to show stratification, and secrete mucus. There is a well-marked increase in leucocytes which may also be found in the lumen of the vagina. (Figure 3.)

Reaction 3. The epithelium of the vaginal mucosa is composed of several layers, and the cells at the surface are of the mucified variety. A characteristic feature often observed is a folding-in of the mucosa, a type

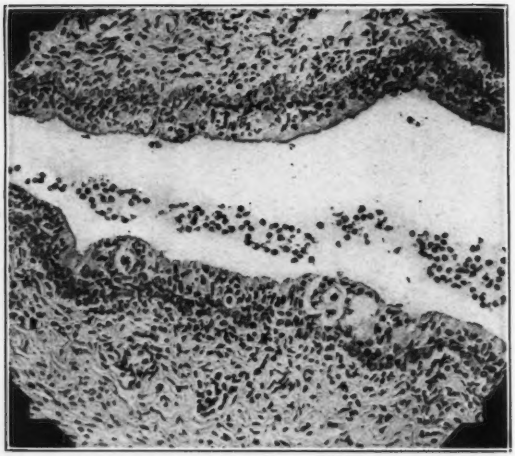

Figure 3. Reaction 2. Mucification well developed, and leucocytes appear.

of festooning, which is evidence of the rapid growth. The mucosa is invaded by large numbers of leucocytes which occur also in the lumen along with epithelial debris. (Figure 4.)

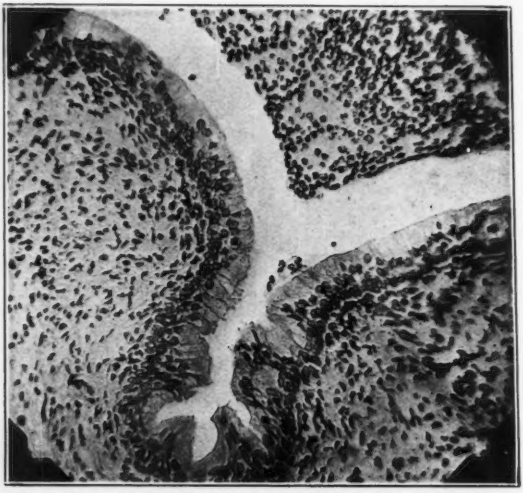

Figure 4. Reaction 3. The epithelium is composed of several layers, mucification is more marked, and there is an extensive invasion with leucocytes.

Reaction 4. The mucosa is made up of from 6 to 10 or 12 rows of cells, the lower resembling the basal cells of squamous epithelium while those at the surface are still of the tall mucified variety. In marked cases early cornification may be observed between the stratified epithelium and the

mucified cells. Leucocytes have disappeared or are present in small numbers. (Figure 5.)

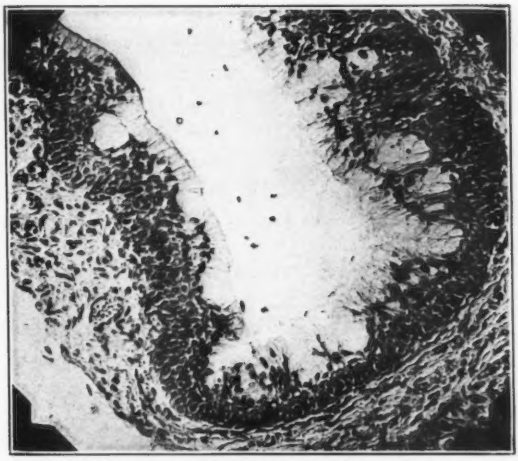

Figure 5. Reaction 4. Marked stratification of the epithelium with mucified cells at the surface, and few or no leucocytes are present.

Reaction 5. The vagina is now lined by fully developed squamous epithelium with cornified cells at the surface. There are no leucocytes.

As in all biological procedures, individual mice vary greatly in their responses to the same dosage. The accuracy of the test thus depends on using as many animals as possible for each specimen. In this work two or three mice has been the minimum employed for each test. After the response for each mouse has been estimated, the numbers are added and then divided by the number of mice used in order to give the reaction. For instance, if three mice are used for a test and reactions 3, 2, and 2 are observed, the reaction elicited by that specimen would be given as 2.3.

CONTROL TESTS

In order to determine the sensitivity of this test a series of 94 mice were injected with known amounts of theelin. Of these, 32 were given aqueous solutions, while the balance received various dilutions of the same potency but made up with horse-serum. The injections were given in the same manner as those for the tests with human blood, and the total amount of horse-serum used was 4.5 cc. in all instances.

The results are given in Table I. The dilution "C" was considered as representing one mouse unit since 5 of 9 mice receiving this preparation developed full cornification of the vagina. The average reaction for each group was determined and this figure gradually diminished as the amount of theelin decreased. For instance, one mouse unit gave a reaction of 4.5, $\frac{1}{4}$ of a mouse unit 2.7, and $\frac{1}{16}$ of a mouse unit 1.4. Six of 10 mice injected

TABLE 1

Dilution	B	C	D	E	F	G	H	Horse Serum
Mouse Units	2	1	½	¼	⅛	1/16	1/32	0?
Reaction 5	7	5						
Reaction 4		4	11	5				
Reaction 3				1	5	3	2	
Reaction 2				2	5	4	4	1
Reaction 1				3	3	4	4	5
Reaction 0					1	4	6	4
Average Reaction	5.0	4.5	4.0	2.7	2.0	1.4	1.1	0.7

with untreated horse-serum gave a slight response, suggesting that it contained very slight traces of some estrogenic substance.

The mice have shown a great variability in their responses to each dilution of the theelin, and in occasional instances it was possible to elicit even 3-plus reactions with as little as $1/32$ of a mouse unit. This is the usual experience with biological tests and points to the importance of injecting as many mice as possible. The results given in the table also demonstrate that the probable error is greater as the amount of estrogenic hormone present decreases.

HUMAN SERA

Over 200 tests have now been conducted to study the estrin content of the blood of women under various conditions. In Figure 6 are given the

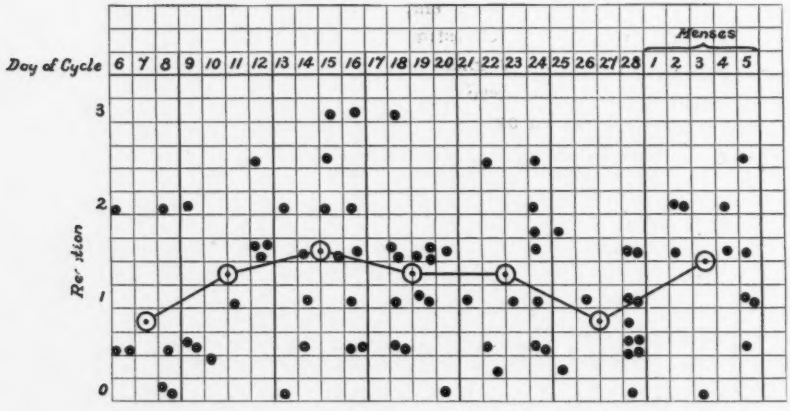

Figure 6. Results obtained from the examination for the presence of estrin of 80 specimens of blood from 46 patients.

results obtained from the examination of 80 specimens from 46 patients. The majority of these individuals were under treatment for gynecologic ailments, but gave a normal menstrual history. The findings are listed

according to the day of the menstrual cycle on which the specimen was obtained. No correction has been made for variations in the length of the different cycles, but as far as could be determined they varied only between 24 and 32 days. A number of tests made two or three days before beginning of the flow in women with cycles over 28 days in length have been recorded as of the 28th day.

It has been possible to demonstrate the presence of estrin in the blood of women at all phases of the menstrual cycle, but a difference has been noted in the concentration present at various times. The cycle has been divided into 7 periods of 3 to 5 days and the average intensity of the tests for each of these has been determined. The resulting curve has been superimposed on the diagram, and it is seen that the greatest concentration of estrin occurred in the middle of the cycle and the early part of the second half, a secondary rise took place at the time of menstruation, and a drop in the amount of estrin present was noted just before and just after menstruation.

Since such a composite curve may be open to objection, it seemed of importance to examine several specimens from the same individual. Four or five specimens obtained at weekly intervals from the same patient have been tested in 11 instances. In nine cases the results corresponded to those noted above, namely, the peak of estrin concentration occurred during the middle of the interval. In one case, small amounts of estrin were present at all times, and a slight rise occurred on the 25th day of a 26-day cycle. Of interest was one patient who gave a 3-plus reaction on the 16th day of a cycle, then had uterine bleeding from the 17th to the 22nd day, gave a minimal reaction on the 23rd day, and had what was considered as her normal menses on what would have been the 24th day.

DISCUSSION

On the basis of the results obtained in this study, this procedure has been adopted in the Stanford Gynecological Laboratory as a means of determining the presence of estrin in the blood of women. The method is now used as part of the examination of patients with various endocrinologic conditions, but it must be emphasized that several tests should be made at various intervals in all individual instances. The small amount of serum required renders this readily feasible. It also may be pointed out that one specimen of 50 cc. of blood may yield enough serum to inject four mice for the estrin test and still leave a sufficient amount to inject two immature mice for the purpose of determining the presence of unduly large amounts of anterior pituitary hormone, as described in a number of previous communications (Fluhmann [3, 16]).

The maximal concentration of estrin in the blood of women during the course of the menstrual cycle has been observed in this study as occurring about one week sooner than previously reported (Frank and Goldberger [17], Siebke [18], Mazer and Goldstein [19], and others), and at a time

when the Frank-Goldberger tests have usually been found negative. It is difficult at present to reconcile these results, but there are a number of important observations which point to the probable correctness of the blood-estrin curve given in this report. (1) Although the exact time relation of ovulation to the peak of estrin production cannot be accurately determined now, they are apparently closely associated. This observation is in keeping with the occurrence of ovulation at the time of estrus, which is the climax of estrin effects, in the lower animals. (2) The intensity of spontaneous rhythmic contractions of excised human fallopian tubes apparently follows that of the estrin curve, since Snyder and Seckinger (2) found the greatest activity in the midde of the interval. (3) The daily excretion of estrin in the urine during the menstrual cycle reached a maximum from 7 to 19 days before the onset of menstruation in most of the women studied by Siebke (21). This would seem to correspond to the time when a maximal concentration has been noted in the blood. (4) The studies of Allen, et al. (22) on the estrin content of human ovarian tissues gave results which are definitely related to the blood findings in this paper. They obtained high yields of the hormone from recent corpora lutea removed on the 13th to the 17th days of the menstrual cycle, and there was a considerable decrease in amount by the 20th to the 22nd day. Although the amount of hormone present in the ovary is not necessarily a true index of the total produced by that organ, the concomitant results are at least very suggestive.

The increase in the concentration of estrin in the blood at the time of menstruation also calls for an explanation, as it is not probable that this is due to an actual renewed production of the hormone. It is possible, however, that it appears because of a release into the circulation of the large amounts which Frank and Goldberger (23) have shown accumulate in the endometrium during the course of the menstrual cycle.

SUMMARY

The technique of a biological test for the demonstration of estrin in the blood has been described. The test depends on the injection of small amounts of untreated serum into spayed mice. A positive result is indicated by the production of a "mucification" of the vaginal mucosa. The method may be applied to quantitative studies, provided a sufficient number of test animals are employed.

The examination of 80 specimens of blood obtained from 46 women at different stages of the menstrual cycle shows that in this series the maximal concentration of estrin was reached during the middle of the interval, a secondary rise occurred at the time of the flow, and it was diminished just before and just after menstruation.

(My thanks are due to Dr. P. E. Hoffmann and other members of the Department for their interest in obtaining the specimens of blood used in this study, as well as to Mr. John J. Kan and Mr. Pierre Lassègues for their technical assistance.)

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PRODUCTION OF OVULATION BY GONADOTROPHIC EXTRACTS*

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The luteinizing and follicular-stimulating fractions of anterior pituitary extracts have rarely been utilized in the ovulation studies which have been made. Furthermore, few studies have been made on immature female animals in which the normal gonadotrophic activity of the animal's own pituitary is thought to be at a minimum.

It was pointed out by Hertz and Hisaw (1934) that ovulation occurred in 45 per cent of the juvenile rabbits to which they administered subcutaneously, first follicular-stimulating and then luteinizing extract, each over a three-day period. Ovulation did not occur in young rabbits treated with unfractionated pituitary extracts, purified follicular-stimulating extracts, or luteinizing extracts alone.

In working with beef pituitaries Evans and associates (1933) reported the failure to produce ovulation in immature female rats by injections of crude extracts, but when their preparations were subjected to further purification ovulation was produced by their administration. It has seemed not unlikely to the author that in further purification of the crude extracts, Evans and co-workers removed a portion of the luteinizing substance which initially prevented ovulation by entrapping the ova in corpora lutea atretica.

Casida and Hellbaum (1934) suggested that the production of ovulation in the immature rat may depend upon a proper balance of follicular-stimulating and luteinizing activities and if too much of the latter is effective the ova are entrapped by rapid luteinization. The experiments which will be reported here have been planned to test further the above suggestion and also to determine what might be a possible mechanism whereby ovulation is effected in the normal mature female.

The sources of hormone for this work were four types of pituitary extracts, namely, unfractionated, purified follicular-stimulating, partially purified follicular-stimulating, and luteinizing, prepared by the method of Fevold, et al. (1933) and also gelding anterior pituitary powder whose gonadotrophic properties were described by Hellbaum (1933). The ovulating properties of these preparations alone and of some of them in combination were tested on 71 female rats, 22 days of age at the beginning of treatment, and on 15 juvenile female rabbits ranging in weight from 1000 to 1400 gm. The occurrence of ovulation was determined by the presence of tubal ova in histological sections of the fallopian tubes of the rat and the

*Aided by grant from National Research Council, Committee on Problems of Sex, administered by Dr. F. L. Hisaw.

†National Research Council Fellow in the Biological Sciences.

presence of macroscopically visible ovulation points on the surface of the ovary of the rabbit, ovulation in the latter condition having been confirmed initially by recovery of tubal ova upon irrigation of the tubes.

EXPERIMENTAL PRODUCTION OF OVULATION IN IMMATURE FEMALE RATS

It was noted previously (Casida and Hellbaum, 1934) that unfractionated extracts of some batches of horse pituitary would produce ovulation in the immature rat, whereas, extracts of other batches caused enclosure of the eggs within the corpora lutea. Inasmuch as Hellbaum (1933) pointed out that a horse pituitary preparation appeared to produce a greater follicular stimulation as compared to luteinization than a similar preparation of sheep pituitary it was decided to test the various types of extracts of sheep pituitary for their ability to produce ovulation. These rats were injected subcutaneously, twice daily for five days, and killed on the sixth day. The ovaries were weighed and histological preparations of the ovaries and tubes made for determinations of the number of corpora lutea and tubal ova.

One group of seven rats was injected with an unfractionated extract, a second group of seven with a partially purified follicular-stimulator, and a third group of eight with a purified follicular-stimulating preparation (Table I). The ovaries of all rats were stimulated as shown either by

TABLE I

PRODUCTION OF OVULATION IN THE IMMATURE FEMALE RAT WITH EXTRACTS OF SHEEP ANTERIOR PITUITARY.

Rat Number	Extract	Ovarian Weight, Mgm.	Number C. L.	Number Tubal Ova
1	1	19	24	0
2	1	21	13	0
3	1	33	30+	0
4	1	45	30+	0
5	1	31	18	0
6	1	14	9	0
7	1	33	30+	0
8	2	22	4	4
9	2	20	4	4
10	2	20	5	5
11	2	23	3	3
12	2	27	7	3
13	2	18	5	0
14	2	16	3	0
15	3	15	0	0
16	3	20	0	0
17	3	10	0	0
18	3	24	0	0
19	3	17	0	0
20	3	11	0	0
21	3	42	0	0
22	3	33	0	0

Extract 1. Unfractionated extract.
Extract 2. Partially purified follicular stimulating extract.
Extract 3. Purified follicular stimulating extract.

increased size and number of large follicles or by the presence of corpora lutea.

No ova were found in the fallopian tubes of the rats receiving the unfractionated extract, although the number of corpora lutea ranged from nine to more than thirty. Ova in various stages of degeneration could be

seen entrapped in many of the corpora lutea, seemingly as a result of very rapid luteinization. When a considerable part of the luteinizer had been removed as was the case with the partially purified follicular-stimulating extract which was administered to a second group of seven rats, ova were found in the tubes of five of the animals. The number of corpora lutea in each of the individuals was small and it would appear that the majority of these corpora were of ovulation and not corpora lutea atretica. The third group received an extract that produced only follicles when administered over a five-day period and showed no tubal ova. These data suggest that a certain amount of the luteinizing substance is necessary for ovulation and that it can be present in large enough amounts to prevent ovulation by too rapid luteinization, thus entrapping the ova. If this is true, it should be possible to produce the conditions noted in the ovaries of the rats treated with the various sheep pituitary extracts by giving combinations of follicular-stimulating and luteinizing preparations.

Inasmuch as the luteinizing preparation was in powder form and not readily soluble in water, it seemed well to use a follicular-stimulating preparation which was in similar form so that the hormone availability might be more nearly comparable. Several individual gelding pituitaries were obtained and powder preparations made of them. These were tested separately on 22-day-old rats and the ones selected that apparently had the least luteinizing effect on the ovaries. Table II shows the results of twice-daily injections for a period of three days of aqueous suspensions of the gelding pituitary powder alone and in combination with the sheep luteinizing powder.

Two strains of rats were available for this experiment and at first animals from both strains were used without suspecting that they were showing a difference in the ovarian reaction. Histological observations in an early stage of the experiment indicated that of the two strains of rats, strain A often showed the presence of corpora lutea and tubal ova, whereas, animals from strain B, similarly treated, seemed to show only follicles and no tubal ova. Altogether 15 animals from strain A and 16 animals from strain B were treated and the number of corpora and tubal ova determined. Nine of the 15 rats of strain A showed the presence of both corpora lutea and tubal ova and another showed more than 30 corpora lutea but no tubal ova. From 5 to 22 ova were found in the tubes of the rats that had ovulated and the ovaries from which these eggs came varied in weight from 15 to 92 mgm. Of the 16 rats of strain B none showed tubal ova and in only one animal was luteinization detected in the ovaries. In that case two rather atypical luteal bodies were noted in the medullary region of the ovary.

There is no evidence as to why the two strains of rats should react differently. It might be suggested, however, that the animals' own pituitaries were secreting more luteinizing principle in strain A than in strain B or that animals of the former strain were more sensitive to the small amount of luteinizing activity exhibited by the pituitary powder. Would it be possi-

TABLE II

PRODUCTION OF OVULATION IN THE IMMATURE FEMALE RAT WITH GELDING ANTERIOR PITUITARY POWDER ALONE AND IN COMBINATION WITH LUTEINIZING POWDER.

Strain A					Strain B				
Rat Number	Dose, Mgm.	Ovarian Weight, Mgm.	Number C. L.	Number Tubal Ova	Rat Number	Dose, Mgm.	Ovarian Weight, Mgm.	Number C. L.	Number Tubal Ova
1	3 GAP	18	6	6	1	6 GAP	31	0	0
2	4 GAP	15	5	4	2	6 GAP	27	0	0
3	5 GAP	16	5	5	3	6 GAP	21	0	0
4	5 GAP	27	11	11	4	6 GAP	16	0	0
5	5 GAP	13	0	0	5	7 GAP	28	0	0
6	5 GAP	16	0	0	6	7 GAP	36	0	0
7	5 GAP	10	0	0	7	7 GAP	32	0	0
8	6 GAP	19	0	0	8	7 GAP	39	0	0
9	6 GAP	36	30	22	9	7 GAP	32	0	0
10	6 GAP	42	28	16	10	7 GAP	42	2?	0
11	7 GAP	44	30+	10	11	7 GAP	25	0	0
12	7 GAP	47	30+	0	12	7 GAP	27	0	0
13	7 GAP	47	30+	21	13	7 GAP	34	0	0
14	15 GAP	47	0	0	14	7 GAP	28	0	0
15	15 GAP	92	Many	6	15	15 GAP	43	0	0
					16	15 GAP	47	0	0
16	6 GAP+ 22 LP	22	10	0	17	6 GAP+ 2 LP	24	0	0
17	"	15	6	0					
18	"	66	Many	0	18	"	46	30+	0
19	"	14	7	0	19	"	18	6	6
20	7 GAP+ 22 LP	83	Many	0	20	"	27	17	11
21	"	62	Many	0	21	"	39	24	13
					22	"	16	5	4
					23	6 GAP+ 9 LP	40	Many	0
					24	"	60	Many	0
					25	"	38	Many	0
					26	"	50	Many	3
					27	"	24	Many	0
					28	"	54	Many	0

GAP=Gelding anterior pituitary powder.
LP=Luteinizing powder (22 mgm. equalling 1 gm. equivalent of acetone desiccated sheep pituitary powder).

ble to inject large quantities of luteinizing substance together with the gelding pituitary powder and inhibit ovulation in strain A where ovulation occurred in 60 per cent of the animals when treated with the gelding pituitary powder alone? This was done with 6 rats which were injected as above with 22 mgm. of luteinizing powder in addition to the dosage of gelding pituitary powder. The weights of the ovaries from these rats ranged from 14 to 83 mgm. and none of them had tubal ova, although there were corpora lutea present in all cases. Retained degenerate ova could be seen in many of the corpora.

Inasmuch as strain B gave follicular stimulation almost exclusively when injected with gelding pituitary powder alone, it was thought pertinent to attempt the production of ovulation in these animals by the addition of small amounts of luteinizing powder. Two mgm. of luteinizing powder were used on 6 animals and 4 of these ovulated. The ovaries of one rat contained more than 30 corpora but no ova were in the tubes; in yet another animal only follicular stimulation was produced. When the dosage of luteinizing powder was increased to 9 mgm., only one rat of six ovulated with three tubal ova and many corpora present.

From the foregoing experiments it seems that a certain amount of the luteinizing fraction is necessary for ovulation. As the amount is increased, however, a point is reached where corpora lutea atretica are produced with the entrapment of ova.

EXPERIMENTAL PRODUCTION OF OVULATION IN IMMATURE RABBITS

Inasmuch as Hertz and Hisaw (1934) had already pointed out the inability of unfractionated sheep pituitary extracts or follicular-stimulating extracts alone to produce ovulation in the juvenile rabbit, the attempt was now made to produce this reaction by injecting a partially purified follicular-stimulating extract from sheep pituitary. Seven juvenile female rabbits ranging in weight from 1000 to 1400 gm. were treated with 1 gram equivalent of acetone desiccated sheep pituitary powder, injections being made twice daily for five days and laparotomies for observation of the ovaries made on the sixth day. Five of the seven rabbits showed one to seven ovulation points.

Intravenous injection of adequate doses of pregnancy urine and anterior pituitary preparations has proven highly efficient in the hands of many workers for the production of ovulation in the mature oestrous rabbit. Apparently it should be possible to bring about ovulation as consistently in juvenile rabbits by producing follicular development with a follicular-stimulating preparation and then giving an intravenous injection of luteinizing extract. Large follicular ovaries were produced in eight rabbits by subcutaneous injection of three-fourths of a gram equivalent of horse pituitary follicular-stimulator over a period of four and one-half days. At the end of that time intravenous injections were made of from 8 to 22 mgm. of luteinizing powder which had been dissolved in a weak aqueous sodium bicarbonate solution. Forty-eight hours later laparotomies were performed and the ovaries examined. All eight of these rabbits had ovulated as shown by the presence in each of six to approximately forty ovulation points. Supplying large amounts of luteinizing substance in presumably a readily available form after many large follicles had been produced in the ovary seemed, therefore, to be highly effective in the production of ovulation in the juvenile rabbit.

DISCUSSION

In the foreging experiments it has been pointed out that in both immature female rats and rabbits the purified follicular-stimulating extract alone produced large follicles in the ovary but did not bring about ovulation. When small amounts of the luteinizing substance were in the extract, and consequently present during ovarian development, ovulation occurred in many animals but the frequency of its occurrence may probably depend upon the relative balance of the follicular-stimulating and luteinizing activities. Such seemed to be the case in both rats and rabbits. The most efficient method of producing ovulation in the immature rabbit seemed to be

in first growing the follicles by means of follicular-stimulating extract and abruptly following that treatment by making a large quantity of the luteinizing substance readily available to the follicles. In the case of both rats and rabbits, the presence of large amounts of luteinizing substance during the course of ovarian development resulted in the formation of corpora lutea atretica without ovulation.

It is, of course, unknown that it is the luteinizing hormone which is specifically necessary for ovulation of the mature follicle. It is possible that some unknown factor is removed from the pituitary extract with the luteinizing hormone during the process of purification of the follicular-stimulating preparation. Such an unknown factor would again enter into the reaction when the luteinizing powder in relatively small amounts is combined with the follicular-stimulating substance, but when the powder is combined in larger amounts the luteinizing activity would gain precedence over the ovulation activity. At the present time, however, it seems to me that it is unnecessary to postulate a specific substance other than the luteinizer as being responsible for ovulation of mature follicles.

Of necessity any attempt to suggest a possible mechanism whereby ovulation is effected in the normal mature female would have to be based upon an explanation of the rhythmical activity of the ovary. The reciprocal interrelationships between the different hormones of the ovary and the different hormones of the anterior pituitary are not yet well enough understood to support an entirely satisfactory theory of the mechanism bringing about the cyclic changes in the ovary.

In the experiments which have been reported, ovulation has been brought about in both the rat and the rabbit by having the luteinizing substance available in low concentrations during the time that the follicles were being matured. Although the proportion of luteinizer to follicular-stimulator in the partially purified follicular-stimulating extracts was relatively low, the amount of the luteinizing activity which was exerted on the developing follicles may have been increased by accumulation with each successive injection until the threshold level of its effect for ovulation was attained at approximately the time that the follicles were mature. The highest incidence of ovulation in the juvenile rabbit was obtained by first maturing the follicles with follicular-stimulator and then introducing adequate quantities of readily available luteinizer while the follicles were yet responding to the follicular-stimulator. The two methods of producing ovulation may be alike in that high concentrations of the luteinizing substance in the blood stream of the treated animals are not attained until the follicles are mature.

A possible mechanism for the normal process of ovulation which these experiments may suggest is that the amount of luteinizing substance which is available to the follicle may be increased when the follicle becomes mature during oestrum. In the rabbit, which does not ovulate spontaneously, the liberation of luteinizer from the anterior pituitary may result from the act

of copulation. In the forms which ovulate spontaneously, the concentration of luteinizing substance in the blood stream may be increased during oestrum through a reciprocal relationship between the pituitary and the ovarian hormones. Explanation of these points must wait, however, until more of the effects of the pituitary hormones on the ovary and the ovarian hormones on the pituitary are known specifically.

SUMMARY

Administration of either unfractionated extracts or purified follicular-stimulating extracts of sheep anterior pituitary failed to produce ovulation in 22-day-old rats. Corpora lutea atretica were present in the ovaries of seven rats treated with the former extract and only follicles in the ovaries of eight rats treated with the latter. Five of eight rats ovulated upon being treated with a partially purified follicular-stimulating extract from which not quite all of the luteinizing activity had been removed.

Gelding anterior pituitary powder alone produced ovulation in nine of fifteen animals from one strain of rats whereas the same powder produced almost exclusive follicular stimulation in sixteen animals from another strain. Addition of 22 mgm. of luteinizing powder to the gelding pituitary powder inhibited ovulation with the formation of corpora lutea atretica in six animals of the first strain, whereas, the addition of 2 mgm. produced ovulation in four of six rats from the second strain. Nine mgm. of the luteinizing powder inhibited ovulation with the formation of corpora lutea atretica in five of six animals from the latter strain.

A partially purified follicular-stimulating extract alone produced ovulation in five of seven juvenile rabbits. Of eight rabbits which were first treated subcutaneously with follicular-stimulator and then injected intravenously with from 8 to 22 mgm. luteinizing powder, all had ovulated within forty-eight hours.

It is suggested that the luteinizing substance is necessary for ovulation of mature follicles but that if the luteinizing activity is too great, corpora lutea atretica will be formed with the enclosure of the eggs in the corpora.

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EXPERIMENTAL STUDIES ON THE HYPOPHYSIS CEREBRI
III. THE EFFECT OF SEVERAL PREGNANCIES IN THE ALBINO RAT

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In a previous study the writer reported the effect of *single* pregnancy (1) and the current study presents the results of an attempt to show by means of careful volumetric, histologic, and statistical methods the changes induced in the hypophysis by *several* pregnancies.

REVIEW OF LITERATURE

Several reviews covering this field have been published recently (1, 2, 3, 4, 5, 6). To these the reader is referred for the bulk of the pertinent literature.

A few contributions that are either not covered in the above or because they present certain interesting facts may be summarized here to advantage.

Agdhur (7) reports that white mice with an increasing number of pregnancies reared on a basal diet show an increase in the weight of the whole hypophysis as well as of its pars anterior and pars posterior, but not in the pars intermedia. In the pars anterior the increase in number of the glandular epithelial cells was increased by about 100 per cent, the volume of the corresponding cells showed an increased growth of about 250 per cent, and the growth of their secreting surface was augmented by about 190 per cent. Among the glandular cells the neutrophils are most increased in number, but the greatest percentage increase (about 290 per cent) is shown by the eosinophil glandular cells.

Wolfe and Cleveland report a drop in the relative percentage of the acidophilic cells (Type I) with a coincident rise in the neutrophilic cells (Type IV) during the first part of pregnancy in the rat, but that during the middle and latter portions of pregnancy the number of acidophils gradually rose and that of the neutrophils dropped. My previous report does not substantiate this fact (1).

In several extensive and carefully analyzed investigations, Rasmussen (3, 8) has found no significant difference in the relative number of the various types of cells in the anterior lobe of the human hypophysis, comparing pregnant with non-pregnant women. He does, however, find a significant difference in the weight of the whole gland in favor of the pregnant group, which increase he has definitely proved to be confined to the anterior lobe.

MATERIALS AND METHODS

The animals used in this investigation consisted of 20 female albino rats (Mus Norwegicus albinus) of standard vigorous Wistar stock and reared in a fashion as described by the author previously (1). The animals were evenly divided into two groups of 10 tests and 10 controls.

The test animals were treated in the following fashion. With the advent of the normal oestrus rhythm, each animal was impregnated and subsequently permitted to suckle its young until the weaning period (21 days), after which they were immediately impregnated again. Upon littering, the young were discarded and all but two animals were impregnated

for a third time. The reason for crowding the pregnancies was to determine if the statement of Erdheim and Stümme (9) could be substantiated experimentally in the rat; namely that the hypophysis of the human multipara is larger than that of the nullipara or primipara, because the histologic changes in the hypophysis during pregnancy are cumulative in nature; that although there is some glandular involution between pregnancies, the tendency for each subsequent pregnancy is to add to the size of the gland, which increment, according to them, is due to a hypertrophy and hyperplasia of the cellular elements.

The test animals were sacrificed on the same day that they cast their last litters to prevent any retrogressive changes from intervening.

The control animals were all virgin females, chosen litter-mates of the test animals and were killed within a day or two of their corresponding mate.

The animals were sacrificed by placing them in a closed jar containing chloroform. The body weight, body length and tail length were recorded. Special care was given to the removal of the hypophysis during autopsy procedure to avoid excess drying or mechanical injury.

The material was preserved in a saturated solution of mercuric chloride to which was added 10 per cent formalin.

The paraffin sections were cut at 5 micra. A volumetric study of the three lobes, a differential cell count, and histologic survey of the anterior lobe were made. For the volumetric procedure the method followed was that of Hammar (10). Every tenth section was mounted and stained with haematoxylin and eosin. The image of each section, magnified 35 diameters, was outlined on paper of uniform thickness, cut out, and weighed on a chemical balance from which the percentage of each lobe was calculated. Agduhr utilized every second section for the volumetric study in his white mice. That every tenth section is sufficient is apparent from the data given in Table I.

TABLE I

DATA INDICATING THE RELIABILITY OF USING EVERY TENTH SECTION

Lobe	All Sections	Every Fifth Section	Every Tenth Section Starting With Section Five	Every Tenth Section Starting With Section One
	%	%	%	%
Animal W30-299 (Absolute weight = 9.2 mg.)				
Anterior	85.65	85.35	85.47	85.26
Posterior	8.58	8.97	8.89	9.05
Intermediate	5.75	5.66	5.64	5.69
Animal W30-312 (Absolute weight = 8.3 mg.)				
Anterior	85.00	85.18	85.74	85.61
Posterior	9.54	9.48	9.61	9.36
Intermediate	5.46	5.34	5.65	5.03

TABLE II

No. of Rat	Age of Rat Days	Body Wt. gm.	Body Length cm.	Wt. Whole Gland mg.	Pars Anterior		Pars Posterior		Pars Intermedia		Capsule and Colloid		Chromophobes		Acidophils		Basophils		No. of Cells Counted	
					Wt.	%	Wt.	%	Wt.	%	Wt.	%	No.	%	No.	%	No.	%	Total	Av. per Field
A.—Absolute and Relative Weights of Lobes of Hypophysis of Control Animals													C.—Differential Cell Count—Anterior Lobe Control Animals							
32–288	233	189	20.2	10.40	8.97	86.3	.92	8.9	.50	4.8	.00	.0	7974	74.2	2397	22.3	372	3.5	10,743	149
32–283	237	194	20.3	11.85	10.53	82.3	.84	6.5	.48	3.7	.95	7.4	6738	71.8	2255	24.0	386	4.1	9,379	134
32–255	274	188	20.6	11.36	9.78	81.5	1.11	9.3	.46	3.9	.64	5.3	7353	73.1	2280	22.7	419	4.7	10,052	144
32–284	240	190	20.8	13.00	11.61	89.3	.92	7.1	.47	3.6	.00	.0	6528	75.4	1725	19.9	410	4.7	8,663	116
32–252	241	212	21.0	11.34	10.05	81.0	.95	7.6	.35	2.8	1.06	8.5	6682	73.2	2252	24.7	190	2.1	9,124	127
32–253	280	200	21.3	13.80	12.66	91.8	.85	6.2	.28	2.0	.01	.1	5894	73.1	1918	23.8	256	3.2	8,068	112
32–303	270	222	21.9	13.03	11.78	82.9	.85	6.0	.40	2.8	1.17	8.2	7370	79.7	1676	18.1	201	2.2	9,247	123
32–296	238	240	22.0	14.63	13.08	87.2	.96	6.4	.59	3.9	.37	2.5	5570	64.5	2644	30.6	424	4.9	8,638	123
32–295	262	220	22.1	11.92	10.60	84.8	.92	7.4	.40	3.2	.58	4.6	5239	64.1	2637	32.3	292	3.6	8,168	117
32–280	240	268	22.8	19.14	17.48	89.2	1.14	5.8	.53	2.7	.46	2.3	7273	79.5	1635	17.9	246	2.7	9,154	131
Average...	251	212	21.3	13.05	11.65	85.6	.95	7.1	.45	3.4	.58	4.3	6662	72.9	2142	23.6	320	3.5	9,124	128
B.—Absolute and Relative Weights of Lobes of Hypophysis of Test Animals													D.—Differential Cell Count—Anterior Lobe Test Animals							
32–285	237	238	21.0	12.83	11.12	84.9	1.22	9.3	.49	3.7	.27	2.1	2635	62.7	3093	34.4	258	2.9	8,986	128
32–258	288	234	21.7	12.59	10.84	86.0	1.11	8.8	.64	5.0	.01	.1	6301	69.4	2440	26.9	339	3.7	9,080	126
32–273	249	235	21.8	13.30	11.66	87.7	1.14	8.6	.50	3.7	.00	.0	5748	73.2	1807	23.0	299	3.8	7,854	109
32–298	262	248	22.0	14.40	12.67	88.0	1.20	8.3	.54	3.7	.00	.0	5953	62.7	3129	33.0	407	4.3	9,489	132
32–259	280	239	22.2	13.11	11.42	85.8	1.22	9.2	.47	3.5	.19	1.4	6948	74.2	2024	21.6	393	4.2	9,365	130
32–297	238	282	22.2	15.52	13.69	86.6	1.31	8.3	.53	3.3	.28	1.8	6888	78.2	1686	19.1	238	2.7	8,806	126
32–269	241	266	22.4	12.21	10.70	86.3	1.03	8.3	.47	3.8	.19	1.6	5171	66.3	2257	28.9	367	4.7	7,795	108
32–276	241	274	22.6	13.38	11.95	86.6	1.00	7.2	.43	3.1	.42	3.0	7030	74.2	2051	21.6	399	4.2	9,480	132
32–279	240	240	22.8	14.20	12.72	89.9	1.07	7.5	.41	2.9	.10	.7	7057	77.5	1805	19.8	240	2.6	9,102	130
32–274	268	248	22.8	13.69	12.18	84.6	1.08	7.5	.43	3.0	.71	4.9	6115	66.5	2716	29.5	370	4.0	9,201	129
Average...	254	250	22.1	13.52	11.90	86.7	1.14	8.3	.49	3.6	.27	1.9	6284	70.5	2300	25.8	331	3.7	8,916	125

It is evident that there is no essential difference whether every section, every fifth section or every tenth section is used. Hence every tenth section has been used, thus eliminating unnecessary work.

For the histologic study and differential cell count, about five sections at regularly distributed intervals were taken, stained a fraction of a minute in ordinary Harris' haemotoxylin to bring out the nucleus, and then with Mallory's (11) triple connective tissue stain (12).

The usual three types of cells were distinguished, namely: eosinophils (acidophils, oxyphils, alpha cells, Type I), basophils (cyanophils, beta cells, Type III), and neutrophils (chromophobes, chief cells, reserve cells, undifferentiated cells, indifferent cells, Type IV). About 9,000 cells were counted in each gland.

No study of the pars tuberalis was made for it had been left attached to the brain during autopsy procedure.

RESULTS

A. Age, Weight and Length of the Animals. Since a definite attempt has been made to kill the litter-mate controls on the same day as the test animals, the average age of the two groups is almost identical, namely, 251 and 254 days, respectively (Table II A, B).

The average body weight of the control animals is 212 grams and of the test animals 250 grams (Table II A, B). That this difference of 38 grams in favor of the pregnant animals is statistically significant is readily determined from Table III. Grossly this difference appeared to be due to an

TABLE III
STATISTICAL CONSTANTS FOR BODY WEIGHT

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	Px100	C. V.
Control	212 ± 9.074	.....	.....	....	12.8
Test	250 ± 7.234	38 ± 11.604	3.274	1.0	10.2

increased amount of adipose tissue in the pregnant animals, and only partly due to actual increase in body length. The body length of the test animals is on an average, 0.8 cm. greater than that of the controls (Table II A, B.), but statistically this difference does not prove to be significant (Table IV).

TABLE IV
STATISTICAL CONSTANTS FOR BODY LENGTH

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	Px100	C. V.
Control	21.3 ± 0.275	.....	.....	....	3.9
Test	22.1 ± 0.526	0.8 ± 0.593	1.348	17.7	7.1

That changes in body size do occur in pregnancy is evident from the review by Engelbach, and is fairly definitely shown in this investigation (Table II, III). However, these size changes are usually due to variations in amounts of adipose tissue and not so much to changes in stature.

The occurrence of acromegalic changes in pregnancy has been reported by Engelbach, Kark (13), Alin (14), Biedl (15) and Jung (16).

B. Weight of the Whole Hypophysis. The average weight of the whole hypophysis for the test animals is only 0.48 mg. heavier than that of the control animals (Table II A, B). This difference does not prove to be significant (Table V). The average weight of the whole gland was obtained

TABLE V
STATISTICAL CONSTANTS FOR WEIGHT OF WHOLE HYPOPHYSIS

Animals	M ± S. E. m.	Diff. ± S. E. Diff.	Diff. S. E. Diff.	Px100	C. V.
Control	13.05 ± 0.787	.....	.....	.....	18.0
Test	13.52 ± 0.309	0.48 ± 0.845	.566	57.5	6.9

by subtracting the weight of the colloid and capsule from the weight of the gland as obtained at autopsy. Including the capsule and colloid, the weights of the control and test glands are practically identical (Table II A, B).

Another point to be considered in the test animals is the significant increase in the body weight (15 per cent), without a corresponding increase in the hypophysis, which increased only 4 per cent or about the same as the slight increase in body length (4 per cent). Apparently the hypophyseal increase follows body length rather than body weight. This correlation of the size of the hypophysis with stature is characteristic of the rat (7, 1) and of man.

C. Absolute and Relative Volume of the Lobes. The anterior and intermediate lobes of the two groups present no significant differences in the absolute or calculated relative weights (Table II A, B). However, the posterior lobe of the test animals shows an average increase of 0.19 mg. over that of the control. This difference is significant, since it can occur by chance, as indicated by P x 100 in Table VI, less than once in a hundred

TABLE VI
STATISTICAL CONSTANTS FOR THE CALCULATED AND RELATIVE WEIGHTS OF THE INDIVIDUAL LOBES

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	Px100	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	Px100
	Pars Anterior (Absolute Weight)				Pars Anterior (Relative Weight)			
Control	11.65 ± 0.765	.....	.....	.....	85.63 ± 1.174	.....	.....	.....
Test	11.90 ± 0.298	0.24 ± 0.821	0.293	76.4	86.65 ± 0.499	1.02 ± 1.276	0.800	42.4
	Pars Intermedia (Absolute Weight)				Pars Intermedia (Relative Weight)			
Control	0.45 ± 0.028	.....	.....	.....	3.35 ± 0.252	.....	.....	.....
Test	0.49 ± 0.021	0.04 ± 0.035	1.262	21.1	3.59 ± 0.194	0.24 ± 0.317	0.749	45.9
	Pars Posterior (Absolute Weight)				Pars Posterior (Relative Weight)			
Control	0.946 ± 0.033	.....	.....	.....	7.11 ± 0.379	.....	.....	.....
Test	1.130 ± 0.031	0.19 ± 0.045	4.268	0.006	8.31 ± 0.229	1.20 ± 0.442	2.703	7.0

times. This increase in size of the posterior lobe is in agreement with Agduhr for the white mouse. However, I find no increase in the size of the anterior lobe such as he and others report in various animals and man (8). One would expect that if pregnancy affects the anterior lobe as markedly as Erdheim and Stümme claim, and especially if these effects were cumulative in nature, that with three rapidly induced, carefully controlled pregnancies, together with utilizing the refined paper weight method, the effects would be easily elicited such as were readily determined for castration effects on the pituitary (17). Using this same technique Atwell (18) found no significant change in the relative volume of the epithelial lobes to accompany the progress of pregnancy in the cat.

D. Relative Number of Different Types of Cells in the Anterior Lobe. Recent studies have tended to strengthen the notion that it is the basophilic cells in the anterior lobe which are primarily related to the sexual functions (2). Many authors overlook this fact when discussing histologic variations in the hypophysis, constantly referring to acidophilic cellular changes, whereas the latter type of cell is evidently related to growth.

Although the percentage of basophils in the rat's hypophysis is relatively small, by meticulously counting enough cells and utilizing careful statistical methods, one can determine if changes in the number have occurred. I find that the basophilic cells comprise 3.51 per cent and 3.72 per cent (Table II C, D) of the total number of cells in the control and test rats, respectively. The difference between these two averages—0.21 per cent—proves to be insignificant statistically (Table VII). These figures

TABLE VII

STATISTICAL CONSTANTS OF PERCENTAGES FOR DIFFERENTIAL COUNT OF CELLS IN ANTERIOR LOBES

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	Px100
Chromophobes				
Control	72.86 ± 1.653	.....	.....	.....
Test	70.49 ± 1.823	−2.37 ± 2.461	0.964	33.7
Acidophils				
Control	23.63 ± 1.509	.....	.....	.....
Test	25.79 ± 1.746	2.16 ± 2.307	0.937	35.2
Basophils				
Control	3.51 ± 0.314	.....	.....	.....
Test	3.72 ± 0.231	0.21 ± 0.390	0.538	58.9

for the pregnant rat hypophysis are comparable to those obtained in the previous study on single pregnancy (3.95 per cent and 3.47 per cent) and to those obtained by Wolfe and Cleveland in the earlier stages of pregnancy in the rat (1-7 days=3.5 per cent; 8-14 days=3.4 per cent; 15-20 days=3.9

per cent). The average of 3.51 per cent basophils found in the control group of this series compares favorably with the control group for single pregnancy (3.36 per cent). Both of these figures are below the average obtained by Wolfe and Cleveland (4.9 per cent) for the normal unmated rat. Statistical constants do not appear with the latter report and consequently it is difficult to properly evaluate their results.

There are on an average about 2 per cent more chromophobes (Table II C, D) and since the number of basophils remain unchanged, correspondingly about 2 per cent less acidophils in the control glands as compared with the tests. However, these differences are not significant (Table VII). This finding is in agreement with that of Rasmussen (3) for the human, but is not in agreement with Wolfe and Cleveland for the rat, or Agduhr for the mouse.

That considerable differences exist in the relative percentage of the various types of cells in the human hypophysis as compared with that of the rat is apparent from the cell counts of Rasmussen (3) (Table VIII), who uses the same staining and counting technique as was used in this series.

TABLE VIII

COMPARISON OF CELL COUNTS BETWEEN HUMAN AND RAT HYPOPHYSES

Author	Series	Neutrophils %	Acidophils %	Basophils %
Rasmussen	Human, non-pregnant	48.2	45.5	6.4
Stein	Rat, non-pregnant	72.9	23.6	3.5
Rasmussen	Human, pregnant	50.1	43.4	6.3
Stein	Rat, pregnant	70.5	25.8	3.7

E. Size of Cells in the Anterior Lobe. No direct measurements of the cells were made. An indirect method can be used to determine if the cells in the two groups of animals differed in size. From 70 to 80 fields of equal size were counted in each gland and the "average number of cells per field" was based on about 800 fields in each group of animals. By comparing the average number of cells per field it is found that there is no significant difference (Table IX). While this is a rough index, it shows that the tre-

TABLE IX

NUMBER OF CELLS PER FIELD IN ANTERIOR LOBE

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	Px100	C. V.
Control	128 ± 1.795	.....	.....	....	4.2
Test	125 ± 2.261	−3 ± 2.887	1.039	30.8	4.6

mendous increase in the size of the cells that occurs in the pregnant mouse (7) does not occur in the rat.

F. Histology. The histologic structure of the two groups of glands can be considered together for no striking differences in morphology could be found between test and control. The tissue was well fixed and stained quite clearly, making it possible to distinguish the three types of cells fairly accurately.

The picture here in no way seems to differ from that described previously for single pregnancy (1).

In agreement with Wolfe and Cleveland for the rat, and Rasmussen (3) for the human, but contrary to numerous others (19, 20, 10), I again found no particular cell type in the pregnant rat hypophysis which could be designated as a "pregnancy cell" (1).

SUMMARY

1. A group of ten virgin white rats were studied in comparison with a group of ten litter mate test animals which had had three pregnancies in rapid succession.

2. The average body weight of the test animals was 38 grams heavier than the controls which proves to be a significant difference; however, the body length of the test animals was not significantly greater than that of the controls, being only 0.8 cm.

3. The average weight of the whole hypophysis in the test group was not significantly greater than that of the control.

4. Evidence is submitted that utilizing every tenth section cut at 5 micra was sufficient to determine the relative size of the various lobes in the rat's hypophysis by the paper weight method.

5. The posterior lobe of the test animals was proved to be increased over that of the controls, but the anterior and intermediate lobes showed no significant differences.

6. A differential count of the cells in the anterior lobe (based on counting about 9,000 cells in each hypophysis) showed no significant difference between tests and controls. The average percentages for the test animals were 70.5 per cent chromophobes, 25.8 per cent acidophils and 3.7 per cent basophils; for the control group the corresponding figures were 72.9 per cent, 23.6 per cent and 3.5 per cent, respectively.

7. The cells in the two groups were apparently equal in size, for the "average number of cells per field" were practically equal in number for test and control.

8. From the standpoint of number, size, shape, nuclear pattern, staining reaction or distribution of cells in the gland, no definite or unique histological feature could be found in the hypophysis of the pregnant group. No special cell which could be designated "pregnancy cell" as described by others for the rat was evident.

The author wishes to thank Dr. C. M. Jackson, Director of the Department of Anatomy, for permission that made this study possible, and wishes to thank Dr. A. T. Rasmussen for the valuable information supplied during the course of the work.

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CORTICOADRENAL INFLUENCE ON BLOOD SUGAR MOBILIZATION

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The adrenal gland, and more particularly the adrenal medulla, has long been associated with variations in blood sugar. Papers on the effects of adrenin (epinephrine) in physiological and pharmacological amounts comprise a voluminous literature that is constantly increasing. We shall not attempt to discuss it in this paper.

In general it is now accepted that increased activity of the adrenal medulla or injections of its active principle result in a rise in blood sugar. Conversely, the low blood sugars found in patients suffering from Addison's disease or in completely adrenalectomized animals have been frequently attributed to loss of the medulla and its adrenin.

We do not agree with the latter view, since it has been shown that dogs (Houssay and Lewis, 1923) and cats (Zwemer, 1924, 1927) having the cortex only of one adrenal survive normally for some time. Furthermore, determinations made on animals so prepared showed that the loss of the adrenal medulla does not greatly affect the blood sugar level of surviving animals. Wyman and Walker (1929) have reported the relation of the adrenal cortex to blood sugar in the rat. Recent emphasis by Britton and Silvette (see bibliography) on the extreme importance of carbohydrate metabolism in adrenal cortex physiology led us to gather together our data* on this subject.

The present writers have extended the observations covering the effects of adrenalectomy on blood sugar and have added their studies on the effects of injections of extracts of the adrenal cortex (cortin†) into both adrenal-insufficient and normal cats. These effects have been compared to those following injections of adrenin and of mixed (cortin and adrenin) extracts. Supplementary, confirmatory data from human and rabbit cases will not be dealt with at this time.

Samples for testing were withdrawn from the heart of the animal or from an ear-vein; and analyzed for blood sugar content by the Folin-Wu

*The first series of animals with cortex only were studied during the summer of 1926 at the Biological Laboratory, Cold Spring Harbor, Long Island, New York, with the assistance of Dr. Mary Shirley. A second series, with a greater number of determinations per cat, were obtained with the aid of Dr. J. M. Smith and the Department of Biochemistry, College of Physicians and Surgeons, Columbia University, in 1929. A brief report was presented before the American Association of Anatomists in April, 1930, at Charlottesville, Virginia (Zwemer, Smith and Shirley, 1930).

Additional data on the effect of partial and total adrenalectomy were obtained with the help of Dr. S. Graff of the Biochemistry Department during the summer of 1929. The senior author takes this opportunity to offer his thanks to the above mentioned individuals and laboratories for their coöperation.

†Cortin is the name suggested by Hartman (1930) for the survival hormone of the adrenal cortex and is selected by us for its brevity. Our undoubtedly incomplete files contain references to sixty-three different methods for making active extracts of the adrenal cortex. Many of these extracts have been given distinctive names by their authors, but the term cortin seems worthy of general use.

or Schafer-Hartman methods. One method only was used for any one group of animals.

At first in the research, we wished to be reasonably sure of the blood sugar level at the time of taking and so used large quantities of blood and made triplicate (Folin-Wu) determinations on each withdrawn sample. Sufficient blood for this type of analysis could be obtained only by cardiac puncture, because in adrenal insufficiency the dehydration of the animal (Zwemer, 1927b) results in decreased peripheral circulation so that even a large vein will not yield free-flowing blood. The mass found in large leg veins of living animals frequently resembles splenic pulp in appearance. The loss of tissue turgor, high red cell counts in the circulating blood of the largest vessels, and the peripheral capillary stagnation further indicate the considerable loss in body fluids. This phase of adrenal insufficiency has been dealt with elsewhere (Zwemer, 1934a).

In a second series, very small amounts of blood were obtained from an ear vein and blood sugar determinations were made by the Schafer-Hartman micromethod. With this procedure, a number of points could be determined during each stage of the operative sequence, but no blood could be obtained from the ear for at least 24 hours preceding death. The findings were essentially the same in both groups of animals, and all subsequent determinations were made by the Folin-Wu method on samples obtained by cardiac puncture.

Difficulties encountered during the course of these studies of adrenal insufficiency were:

(a) *The Age of the Animal.* Elliott and Tuckett (1906) stated that kittens did not survive the removal of one adrenal. We have found that even the removal of part of one adrenal is fatal in kittens. Although they may survive the operation by two or three weeks, the growing animal evidently needs its full complement of adrenal tissue. This is further emphasized by the occasional death of young (¾ grown) cats three or more weeks after unilateral adrenalectomy. These animals show the typical symptoms and postmortem examination reveals the pathologic histology found in other cases of adrenal insufficiency. The data in this paper are from adult, male cats.

(b) *Removal of Too Much Adrenal Cortex.* In these cats, too much cortex was removed in the attempt to make sure that no medullary tissue remained in the gland. The animals died a few weeks after the operation in spite of the presence of some easily identified cortico-adrenal tissue.

(c) *Respiratory Infections.* We have observed, and confirmed by postmortem examination, the fact that animals suffering from adrenal insufficiency are particularly susceptible to respiratory infections. A wave of respiratory infection may occur even though each animal is in a separate cage and the room is kept at a constant temperature. It may prove to be rapidly fatal to all animals suffering from complete and many with partial adrenal insufficiency. Naturally, animals so affected could not be included

in our test observations as we have previously shown that the white blood cell picture (Zwemer and Lyons, 1928) and pathologic histology (MacMahon and Zwemer, 1929) is not typical of adrenal insufficiency in these cases.

The experimental results fall naturally into two main divisions. We will deal first with the effect of degrees of adrenal ablation on blood sugar and later with the changes that follow the injection of extracts into adrenalectomized and normal animals.

Our normal control determinations number nearly one hundred, and average 106 mg. per 100 cc. of blood. The greatest number (over 90 per cent) of the figures fall between 80 mg. and 120 mg. per cent (Table 1).

BLOOD SUGAR TABLE 1

DEGREES OF ADRENAL ABLATION

	Normal	One Adrenal Medulla Out	One Entire Adrenal Out	One Adrenal and Other Medulla Out	Both Adrenals Out
Number of cats	56	23	11	10	31
Number of determinations	95	26	16	19	50
Range of greatest number of determs.	80–120 mg.	80–125 mg.	80–115 mg.	80–100 mg.	50–100 mg.
Maximum	137 mg.	145 mg.	130 mg.	133 mg.	122 mg.
Minimum	70 mg.	67 mg.	77 mg.	70 mg.	44 mg.
Median	104 mg.	106 mg.	102 mg.	102 mg.	81 mg.
Average	106 mg.	103 mg.	95 mg.	94 mg.	78 mg.

The removal of one adrenal medulla does not seem to have had any depressing effect on the blood sugar level (average 103 mg. in 23 cats). This holds in spite of the fact that the operation involves temporary occlusion of the blood supply of the gland while the latter is being split open, the medulla and innermost portions of the cortex scraped out with a curette and the remaining corticoadrenal halves stitched together again (Zwemer, 1927a).

The simpler operation of removal of one entire adrenal has in most cases a slight lowering effect (average 94.5 mg. in 21 cats). This occurs regardless of whether the animal still retains one entire adrenal or only the cortex of one adrenal. We associate this 10 per cent decrease in blood sugar with the loss of half of the animal's corticoadrenal tissue, since the removal of half the medullary tissue has no such effect.

Furthermore, the cortex of one adrenal in the absence of medullary tissue is sufficient to hold the blood sugar above the lower limits of normal (average 94 mg. in 10 cats).

Removal of the remaining corticoadrenal tissue is followed by an additional lowering of the sugar level. The decrease is not prevented by the presence or absence of medulli-adrenal tissue nor by accessory chromophile tissue. In other words, a definite drop in blood sugar occurs regardless of whether complete adrenalectomy results from removal of the second entire adrenal or of the cortical remnant that has been maintaining life (average 78 mg. in 31 cats).

The time interval after cortico-adrenalectomy assumes importance when we examine a redistribution of some of the previous figures (Table 2). They indicate that in addition to the initial change a further decrease may occur some days later.

BLOOD SUGAR TABLE 2
TIME INTERVAL AFTER ADRENAL CORTEX REMOVAL

	Normal	Removal of One Adrenal Cortex		Complete Cortico-Adrenalectomy	
		1st to 10th Day	11th to 30th Day	1st to 4th Day	5th to 11th Day
Number of cats	56	17	8	27	17
Number of determinations	95	19	16	33	17
Range of greatest number of determs.	80–120 mg.	80–115 mg.	80–100 mg.	55–105 mg.	50–90 mg.
Maximum	137 mg.	133 mg.	111 mg.	122 mg.	95 mg.
Minimum	70 mg.	70 mg.	74 mg.	44 mg.	45 mg.
Median	104 mg.	102 mg.	93 mg.	83 mg.	70 mg.
Average	106 mg.	97 mg.	92 mg.	83 mg.	69 mg.

The extremely low blood sugars appearing after adrenalectomy are generally terminal, although a few of our cats had a definite hypoglycemia for four or five days before death. This is shown by a more detailed study of the daily averages following removal of both adrenals (Table 3A).

BLOOD SUGAR TABLE 3A
DAILY TABULATION OF FIFTY-EIGHT DETERMINATIONS AFTER COMPLETE ADRENALECTOMY (NO TREATMENT GIVEN)

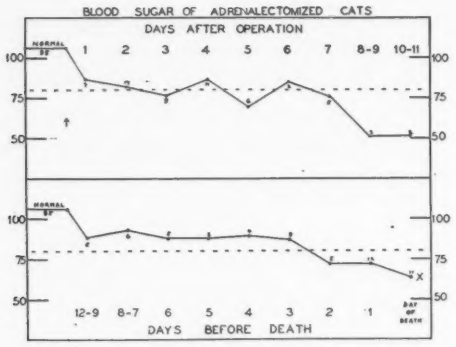
Days After Operation	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th
Number of cats	7	14	9	11	6	2	5	1	1	1	1
Highest	101 mg.	122 mg.	102 mg.	110 mg.	87 mg.	91 mg.	95 mg.	.....	.....	.....	.....
Lowest	69 mg.	44 mg.	52 mg.	53 mg.	52 mg.	78 mg.	62 mg.	.....	.....	.....	.....
Median	85 mg.	83 mg.	77 mg.	82 mg.	70 mg.	85 mg.	79 mg.	.....	.....	.....	.....
Average	86 mg.	82 mg.	76 mg.	87 mg.	69 mg.	85 mg.	77 mg.	57 mg.	45 mg.	54 mg.	50 mg.

These determinations are from animals with straight adrenal insufficiency, uncomplicated by treatment or demonstrable intercurrent infection. A better indication of the true course of events is obtained by a redistribution of these figures according to days before death (Table 3B). The graphic

BLOOD SUGAR TABLE 3B
SAME DATA AS ABOVE REARRANGED

	Days Before Death							Day of Death
	7–12	6	5	4	3	2	1	
Number of cats	11	5	2	4	9	5	12	11
Highest	128 mg.	106 mg.	122 mg.	106 mg.	102 mg.	90 mg.	95 mg.	87 mg.
Lowest	67 mg.	80 mg.	53 mg.	67 mg.	71 mg.	45 mg.	50 mg.	44 mg.
Median	98 mg.	93 mg.	88 mg.	87 mg.	87 mg.	68 mg.	73 mg.	66 mg.
Average	91 mg.	88 mg.	88 mg.	91 mg.	87 mg.	72 mg.	72 mg.	64 mg.

representation of these data (Graph I) reveals an initial drop, followed by a plateau at the lower limits of normal for some days and finally another decrease. Exceptions to the average are present in both early and later



GRAPH 1

adrenal insufficiency. The blood sugar can be 53 mg. per cent five days before death, or 87 mg. per cent on the day of death. The relation of the adrenal cortex to blood sugar is of definite but not critical importance.

Sugar reserves are present for a week after adrenalectomy. With the proper stimulus this reserve sugar can be mobzilized into the blood stream very quickly. Excitement, adrenalin and adrenal cortex extracts all initiate increases in blood sugar (Table 4). For a given stimulus the increment in

BLOOD SUGAR TABLE 4

MOBILIZATION OF BLOOD SUGAR IN TWELVE ADRENALECTOMIZED CATS

Day After Adrenal-ectomy*	Cat Number	Blood Sugar Before Stimulation	Highest Sugar After Stimulation	Number of Samples Taken	Amount and Type of Stimulus
		mg. %	mg. %		
1	H 20	91	133	4	Excitement.
1	M 54	89	116	4	1 cc. of 1/100,000 adrenalin P. D.
1	M 53	69	81	4	1 cc. of 1/10,000 adrenalin P. D.
2	M 53	81	256	3	3 cc. of 1/1,000 adrenalin P. D.
2	M 52	78	92	4	1 cc. of 1/10,000 adrenalin P. D.
2	L 21	112	253	5	1 cc. adr. cort. extract VIII 1, 2, 3.
2	L 7	90	283	6	2 cc. of adr. cort. extract IV.
2	L 8	102	357	2	0.2 cc. of adr. cort. extract V conc.
3	M 51	72	93	4	1 cc. of 1/100,000 adrenalin P. D.
3	M 50	(148)†	170	5	1 cc. of 1/10,000 adrenalin P. D.
4	M 50	80	206	3	1 cc. of 1/1,000 adrenalin P. D.
4	L 14	90	263	5	1 cc. of adr. cort. extract V dilute.
7	L 50	71	125	3	3 cc. of adr. cort. extract XII.
7	L 13	95	182	4	2 cc. of adr. cort. extract V dilute.
Averages before.....		86	186 and after stimulation		

*All except H20 lived for at least six days after adrenalectomy, in spite of repeated blood sampling.

†Became excited before control blood was obtained, cf. H20.

an adrenalectomized cat is not as great as that for a normal animal. In the cases M50 and M53 a weak stimulus failed to give an impressive rise but on the following day we obtained marked hyperglycemia with a stronger stimulus. The reserve is present and demonstrable for at least seven days after complete adrenalectomy (L13 and L50).

In our adrenalectomized animals we noted a difference in the action of the hormones of the adrenal on the height and duration of the blood sugar rise. These differences also appear when extracts are given to normal animals (Table 5).

BLOOD SUGAR TABLE 5
EXTRACTS TO NORMAL CATS

A.—CONTROLS.

No. of Cats	Time Relation to Injection	Before		Injection	After						
		24 Hrs.	5–30 Mins.		5–30 Mins.	1 Hr.	5 Hrs.	12 Hrs.	24 Hrs.	48 Hrs.	72 Hrs.
		mg. %	mg. %		mg. %	mg. %	mg. %	mg. %	mg. %	mg. %	mg. %
9	Group I	....	94	†	104	....	102	....	103	105	108
50	Group II*	88	90		....	....	....	....	92	91	....

B.—ADRENALINE.

5	1/1,000 1 cc	....	102		222	328	400	....	112	130	....
	1/10,000 1 cc	....	103		168	268	122	....	107	115	....
	1/100,000 1 cc	....	82	†	128	106	95	....	100	130	....
	1/100,000 1 cc	....	133		161	141	....	....	110	114	....
	1/1,000,000 1 cc	....	129		129	133	....	....	143	....	....

Height and duration of rise depended on strength of injection. Strongest was normal in 24 hours.

C.—CORTIN (single injection).

30	Highest	....	137		162	270	488	....	137	133	130
	Lowest	....	81	†	93	103	72	....	75	60	93
	Median	....	109		127	186	280	....	106	97	112
	Average	....	108		122	141	146	....	111	103	108

Height and duration of individual cases were obliterated by averaging in this manner.

D.—MIXED (Cortin with Adrenin).

37	Highest	....	150		513	416	375	270	143	143	121
	Lowest	....	88	†	67	100	95	74	66	83	84
	Median	....	119		290	258	235	172	104	113	102
	Average	....	104		181	256	218	133	105	103	100

More rapid high rises (Adrenin). Better prolongation (Cortin).

*This group of cats had been used in blood studies for over a year. This might account for their slightly lower average blood sugars.

In 59 controls we failed to obtain rapid or prolonged changes in blood sugar, although varying amounts of a number of substances were injected (Table 5A).

For our own benefit we retested the effects of adrenalin in five cases (Table 5B), using different dilutions of the extract. We confirmed the finding that the height and duration of the sugar rise is proportional to the strength of the injection and that the return to normal is relatively rapid.

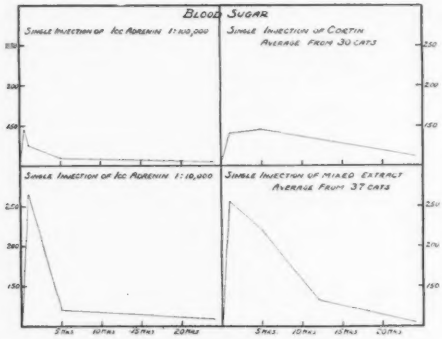
In thirty cases, cortin† gave a slower increase in blood sugar than adrenin and the rise was maintained for some hours before a decrease began (Table 5C).

Our earlier crude extracts contained both cortin and adrenin; these gave a mixed action in which the effects of the two types were combined

†See footnote on Page 730.

(Table 5D). The rapid high rises induced by adrenin were maintained at a fairly high level with the prolonging action of the cortin. This double effect of mixed extracts has been previously commented on in discussing the relation of corticoadrenal hormone to the CO_2 capacity (Zwemer and Sullivan, 1931; Zwemer, 1931).

A graphic presentation of the above data brings out the distinction between adrenin, cortin and mixed extracts. In both cases a comparison has been made with an amount of adrenin giving a similar peak rise (Graph II.) In the case of adrenin and cortin, the latter is reaching its peak as the


BLOOD SUGAR
SINGLE INJECTION OF 1CC ADRENIN 1:10,000
SINGLE INJECTION OF CORTIN
AVERAGE FROM 30 CATS
SINGLE INJECTION OF 1CC ADRENIN 1:10,000
SINGLE INJECTION OF MIXED EXTRACT
AVERAGE FROM 37 CATS

GRAPH 2

former is returning to normal. With mixed extract there is again a slow return to normal, although the initial rise is as rapid as that produced by adrenin alone. The chief difference between adrenin and cortin effects on blood sugar is the slow return to normal after cortin. In some cases, particularly in adrenal insufficiency, the initial response to cortin may occur within a few minutes, but the hyperglycemia, unlike that produced by adrenin, is prolonged.

DISCUSSION

The lowered blood sugar in adrenal insufficiency is due to a lack of cortex and not of medulla. Our extirpation experiments indicate the importance of the corticoadrenal tissue in the maintenance of a high normal blood sugar level. This was first found to be true for the rat by Wyman and Walker (1929) and for the cat by Zwemer, Smith and Shirley (1930).

The profound changes in blood sugar, emphasized by Britton and Silvette (1932b, 1933) are nearly always terminal phenomena. Rogoff and Stewart (1926) found that this was the case in the adrenalectomized dog. Shortly before death a number of equally important blood chemical changes appear which are also incompatible with life (Zwemer and Sullivan, 1931, 1934).

Sugar reserves are present in the body for a week after complete adrenalectomy and can be rapidly (5 minutes) mobilized with an adequate stim-

ulus. In these results we differ somewhat from Britton (1933), who believes that "carbohydrate mobilization is impossible" in adrenalectomized animals.

We have not determined the location of these reserves nor the method of mobilization. They cannot be transported, however, without movements of body fluids, i.e., blood, lymph and extracellular tissue juices.

Although hydration of certain tissues has been reported in the adrenal-insufficient rat (Silvette and Britton, 1933), there is no record as to whether this was due to "free" or "bound" water. Furthermore, the picture of complete and uncomplicated corticoadrenal insufficiency is difficult to obtain in the rat, because of the frequent presence of large and small accessory cortical nodules. The functional value of the nodules is also difficult to determine because size is no criterion of adrenal cortical activity (Zwemer, 1934b). In many experiments we have noted also that the presence of a small amount of cortical tissue makes considerable difference in the reaction of an animal to test procedures.

In spite of an increased water content of certain tissues we believe that the body as a whole loses salt and water. A few years ago we showed that "the chemical picture—of adrenal insufficiency in animals is that of a disturbance of salt and water metabolism" (Sullivan, MacLean and Zwemer, 1932). This preliminary report has been confirmed both experimentally and clinically. Also it is well known that in uncomplicated adrenal insufficiency of cats and dogs there is a definite loss in body weight. In long-surviving animals this loss may amount to as much as 25 per cent of the preoperative weight. Since even in muscle the proportion of carbohydrate is only 0.3 per cent, the loss in body weight must be due to something else. If this is not water, and living organisms are 75 per cent water, one would indeed have a very dilute solution to autopsy. We find on the contrary, the body is markedly dehydrated (MacMahon and Zwemer, 1929).

We agree with Britton and Silvette (1931b, 1932a) that cortin and adrenin differ in the speed, degree and duration of their effects on blood sugar. Our results indicate that adrenin initiates a rapid, high rise of short duration, whereas a cortin injection is followed by a slower, moderate but prolonged increase. Injections of mixed extracts give a combination of the two effects. It seems reasonable to suppose that they mobilize sugar by different methods.

SUMMARY

The influence of the adrenal cortex on blood sugar has been studied by an analysis of determinations on approximately 850 blood samples from more than 195 cats.

The determinations after different degrees of adrenal removal (Table 1) indicate that removal of corticoadrenal tissue has a more pronounced effect on blood sugar than medulliadrenalectomy. There is a correlation between the time interval after adrenal cortex removal and the degree of hypoglycemia (Table 2).

Although a definite decrease in the blood sugar level follows complete adrenalectomy, a daily analysis (Table 3) shows that the average figures remain within the lower limits of normal for some days (Graph I). The profound changes are essentially terminal, but a few animals have had marked hypoglycemia for four or five days before death, while others were normal on the day of death.

Depletion of reserves is not responsible for low blood sugar in adrenal insufficiency. Excitement, adrenalin, cortin and mixed extracts can all rapidly mobilize sugar into the blood stream (Table 4).

A difference in the influence of adrenal cortex and of adrenal medulla on blood sugar is suggested by figures from 131 normal cats (Table 5). Injections of control substances produce no great or constant change during 72 hours. Adrenalin induces the well-known rapid rise and fall in blood sugar, the height and duration of the rise being proportionate to the amount given. Cortin produces a relatively slow rise and slow fall. Mixed (cortin and adrenin) extracts produce a rapid rise and a slow fall in blood sugar (Graph II).

The relations of the adrenal cortex to carbohydrate mobilization, to electrolyte metabolism and to other biomechanisms should be treated simply as expressions of its fundamental importance in the maintenance of life itself.

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Abstract Department

The function of the adrenal medulla. Annau, E., S. Huszak, J. L. Svirbely and A. Szent-Györgyi, J. Physiol. **76:** 181. 1932.

Under certain conditions, trichloracetic acid extracts of ox suprarenal glands contained a substance having a more potent pressor action on the blood pressure of cats (decerebrated, decapitated or etherized) and also a more potent inhibiting action on the isolated rabbit intestine than adrenaline. The adrenaline content of these extracts was estimated colorimetrically but the potency of the extract was found to be 10-15 times higher than that of the adrenaline content alone. The authors propose to call this new substance "Novadrenine."—Caroline Tum Suden.

Researches on carotene; carotene of the adrenal gland (Recherches sur la carotene; Carotene des glandes surrenales). Bailly, O. and R. Netter, Bull. Soc. chim. biol. **14:** 623. 1932.

A technique for extraction of carotene in crystalline form from whole gland, cortex and medulla of beef adrenals is described. The yields obtained were 1 cgm./kgm. and a negligible quantity, respectively. The point of fusion of the crystals is 192 degrees. It is indicated that the carotene of the adrenal gland as of the ovary, is composed of or is very rich in isomer β. The properties are the same as those of vegetable carotene. The author believes that the presence of carotene in the adrenal may contribute to the explanation of the anti-infection function of the adrenal cortex.—J. E. Lockwood.

The treatment of coughs with suprarenal; whooping-cough; preliminary report. Barbour, O., Arch. Pediat. **49:** 816. 1932.

The author reports on the use of suprarenal extract, gr. ½ with thyroid extract gr. ¼ every three hours by mouth. Either aolan or omnadin (2 cc.) was added in some instances. Of the 85 cases treated, excellent results were obtained in 95%. In 50% of the cases, striking amelioration of the symptoms was noted in one or two days and a complete disappearance of the cough in one to four weeks following the use of suprarenal. In 20% prompt relief followed the use of thyroid and suprarenal. In four cases (5%) the treatment had little or no effect.—M. B. G.

The action of adrenal cortex extracts on blood cholesterol (Die Einwirkung des Nebennierenrindenextrakts auf die Cholesterinämie). Collazo, J., G. Marañon, E. Roda and Isabel Torres, Endokrinologie, **13:** 186. 1933.

By the use of freshly prepared assayed extracts a hypercholesterolemic action of adrenal cortex was demonstrated in rabbits, dogs, normal human subjects and in patients with various disorders.—M. O. L.

The adrenals in muscle glycogen recovery after fatigue (Papel de las suprarrenales en la reconstitución del glucógeno muscular después de la fatiga). Dambrosi, R. G. and L. F. Leloir, Rev. Soc. argent. de biol. **9:** 408. 1933.

Adrenalectomized dogs occasionally had low values for resting muscle glycogen 48 hours after adrenalectomy. Under chloralose anaesthesia the sciatic nerve was stimulated peripherally with a tetanizing current for 15 minutes. Muscle glycogen was determined in 3 muscles (Tibialis anticus, Gastrocnemius and Extensor digitis) immediately after the tetanus and after 1 hour of complete rest. Of 8 dogs adrenalectomized 24 hours previously, 3 had normal glycogen recovery, 4 showed a slight recovery and 1 did not recover its glycogen storage. Of 4 adrenalectomized 48 hours previously, only 1 had a slight increase.—J. T. L.

Addison's disease with so-called atrophy of the adrenal cortex. Duff, G. L. and C. Bernstein, Bull. Johns Hopkins Hosp. **52:** 67. 1933. Abst., Arch. Path. **16:** 569.

Five cases of Addison's disease, in four of which the patient had been treated with extract of suprarenal cortex, are reported. All of the patients showed more or less complete "atrophy" of the suprarenal cortex. The destructive process in the suprarenals consisted of a progressive necrosis of cortical cells with collapse of the stroma. In two cases there was regeneration of cortical tissue. The medulla was affected much less, usually showing only a slight increase in the density of the fibrous framework and some shrinkage of the medullary cells. Lymphocytic infiltrations were constantly present in the suprarenal medulla and among the remnants of cortical tissue. Lymphocytic infiltrations in various situations constituted the most constant findings in association with the suprarenal lesions. Marked hyperplasia of lymphoid tissue was not present. No lesions were found for which the treatment with extract of suprarenal cortex could be held responsible. Consideration of the possible etiologic factors in the suprarenal lesions leads to the conclusion that a circulating toxin of unknown origin and nature was probably the causative agent. A brief account is given of observations on four cases in which the early stages of destruction of the suprarenal cortex were found but no clinical evidence of Addison's disease. The findings indicated that the primary suprarenal lesion is in the cortex and that the three zones of the cortex differ in their susceptibility to damage.

Hypertrophy of the adrenal glands following administration of pituitary extract. Emery, F. E. and W. J. Atwell, Anat. Rec. **58:** 17. 1933.

Using 101 albino rats, approximately half of which were controls, marked enlargement of the adrenal glands was produced in normal and castrated males by ten daily injections of sheep whole pituitary extract in 0.5 and 1.0 cc. amounts. The increase, which amounts to as much as 118% in castrated rats treated with the larger dosage, is principally in the cortex, although there is also a less marked enlargement of the medulla. Histologically the cortex shows hypertrophy of its cells, especially those of the inner and intermediate zones. The nuclei are normal in appearance. Few mitotic figures are seen. The cytoplasm is crowded with an unusually rich content of lipoid material. Seven rats injected with a suspension of rat brain in normal saline showed less than 10% larger adrenals than an equal number of uninjected controls. Ten daily injections of 25 to 100 R.U. of antuitrin-S, a preparation made from the urine of pregnant women, did not produce any apparent change in the adrenals of castrated male or female albino rats.—W. J. A.

Does denervation of the adrenal glands cure experimental pancreatic diabetes (L'énervation des capsules surrénales guérit-elle le diabète pancréatique expérimental)? Gondard, L., Compt. rend. Soc. de biol. **112:** 1036. 1933.

One dog was subjected to a total pancreatectomy, removal of one adrenal, and denervation of the other. He lived 12 days during which time he was diabetic. Another dog, similarly treated except that a bit of pancreas was left in place, lived 8 months and was likewise markedly diabetic. Denervation of the adrenals, therefore, does not affect experimental pancreatic diabetes.
—J. C. D.

Certain functions of the adrenal cortex. Hartman, F. A., New England J. Med. **209:** 480. 1933.

An account of the possible functions of cortin is given, based upon observations in man and animals. Cortin plays an important rôle in the nervous, muscular and circulatory systems because without it asthenia of these systems develops. Its importance to the renal, gastro-intestinal and gonadal systems is discussed. General aspects of cortin function are the influence on metabolism, growth, skin changes and resistance to toxins. A newly discovered function of cortin or some unidentified substance in the adrenal cortex is the part it seems to play in the utilizations of vitamins B_1 and C. When an extract of adrenal cortex is injected, it improves the growth curves and delays the onset of symptoms in avitaminosis B. It also improves the growth curve and delays scurvy development in vitamin C deficiency, but has no effect in vitamin A deficiency. Since cortical extract retards the onset of avitaminosis symptoms of vitamins B_1 and C, it is suggested that an ample supply of these vitamins would be advantageous in adrenal cortical insufficiency. Cortin seems

to have such a wide influence on the tissues of the body that it may be considered as a general tissue hormone. Evidence for a lactation hormone of the adrenal cortex is presented.—J. C. D.

Pressure on the eyeball and the discharge of adrenaline (Compression des globes oculaires et décharges d'adrénaline). Hermann, H., L. Merklen, D. Santenoise and M. Vidacovitch, Compt. rend. Soc. de biol. **112:** 1075. 1933.

The adrenal vein of one dog was anastomosed with that of a second animal. Compression of the eyeball in the donor caused contraction of the spleen in the receptor with other signs of adrenaline discharge.—J. C. D.

Suprarenal cortex and sexual development (Nebennierenrinde und Geschlechtswicklung). Loos, H. O. and R. Rittmann, Endokrinologie, **13:** 82. 1933.

In view of the contradictory reports that the suprarenal cortex contains a principle which either is protective to the male sex function and stimulates the female gonads, or which inhibits the male sex function, the following experiments were made. In one series male rats were fed with dried or fresh cortical material, or injected with extracts, either alone or in addition to the feeding (8 experiments, 25 rats). In some cases daily, subcutaneous injections of a 0.1 N HCl extract were given; in others from 0.1 cc. to 1.0 cc. of "Cortisupren" (treated from 22 to 34 days). In addition castrated cocks were also fed cortical material and compared with castrated controls. In a second series of 32 male and female rats two to four abdominal implants of rat cortical tissue (homoplastic) were made every 2-10 days in an attempt to produce a state of "hypercorticalism." These treated rats were then compared with normal litter mates, or with castrated litter mates, to ascertain any difference in growth or sex development. It was found that the series of fed or injected animals were slightly heavier than the controls in most cases. No evidence was obtained that cortex administration stimulated the male gonads. If anything, there was some indication of an inhibiting effect. In the implanted series no conclusive proof of the existence of a male-inhibiting and female-stimulating principle of the cortex was obtained—since such changes as were observed could be attributed to non-specific effects of implanted tissue or normal variations.—L. C. W.

The internal secretion of the adrenal cortex (Über die innere Sekretion der Nebennierenrinde). Schmitz, E. and J. Kühnau, Biochem. Ztschr. **259:** 301. 1933.

Since it was shown in earlier work that extracts of the adrenal cortex made by different methods have diverse effects on the cholesterol and phosphatid content of plasma, in normal rabbits and in doves with avitaminosis-B, the cortical secretion must be not a single substance, but three: a phosphatid-increasing factor, a cholesterol-decreasing factor, and a phosphatid-decreasing factor. Methods are described for separating these three factors, called, respectively, A, B, and C. These may be obtained in pure form by vacuum distillation at definite boiling points. The distillates are bright yellow oils, which the authors believe are chemically pure substances. The results of analyses for C, H, and O are given, together with suggested empirical formulae for Factors A and B. Tables are given, showing that each factor, when injected into normal rabbits, has its characteristic effect on the plasma cholesterol or phosphatid. A fourth factor, a cholesterol-increasing factor, is needed to complete the series, and the authors believe this is adrenaline; with large doses after a considerable time (24 hours), they find a significant increase in plasma cholesterol with adrenaline. The authors suggest that the secretion of these factors by the adrenal may comprise the regulatory mechanism for lipoid and fat metabolism. They discuss the possible identity of their Factor B with the vital hormone in extract prepared according to the method of Swingle and Pfiffner. With the latter, they obtained a decrease in plasma cholesterol; the solubilities of the two are the same; in a vacuum desiccator, an oil similar in appearance to their own is obtained from the extract of the Swingle and Pfiffner method. It was not determined whether the isolated factors will maintain life in adrenalectomized animals, but such a report is promised in the near future. A number of patients with hypercholesterolaemia associated with nervous affections were treated with Factor B, and the hypercholesterolaemia was relieved. The name proposed for the extracts is Supracortin A, B, and C.
—C. A. Winter.

The influence of partial and total adrenalectomy on the results of diabetic piqûre of the bulb (Influence de la surrénalectomie partielle ou totale sur les effets de la piqûre diabétique du bulbe). Vidal, J., Compt. rend. Soc. de biol. **112:** 762. 1933.

In eight rabbits, diabetes did not appear after piqûre when one or both adrenals had been removed.—J. C. D.

Hormones in cancer; the effect of glandular extirpation upon the growth of transplantable tumors. Bischoff, F. and L. C. Maxwell, J. Pharmacol. & Exper. Therap. **46:** 51. 1932.

The authors find that splenectomy, adrenalectomy, thyroparathyroidectomy and castration do not significantly affect the growth behavior of the R 10 sarcoma or the carcinoma (256) in rats. From 13 to 29 rats were included in each series with an approximate number of litter mates as controls. Young animals were used throughout, with inoculation of the tumors a few days after the operative procedures.—R. A. Phillips.

Changes in the interferometer readings (method of Hirsch) in the course of the menstrual cycle (Variations des résultats interférométriques [méthode Hirsch] au cours du cycle menstruel). Desaux, A. and C. O. Guillaumin, Compt. rend. Soc. de biol. **112:** 751. 1933.

The activity of the different endocrine glands in a patient can be measured according to the authors by testing the activity of the blood on extracts of the kind of gland to be examined. The "activite fermentaire" is measured by the interferometer. This article gives the changes as followed by this method.
—J. C. D.

Hemochromatosis. Gott, R., Jr., J. A. M. A. 101: 1874. 1933. Abst., A. M. A.

The author presents a case of hemochromatosis that has been under observation for six years, in which at the time of death there was an abundance of hemosiderin in the liver, pancreas, lymph nodes and suprarenals. Apparently the pigmentation of the pancreas resulted in necrobiosis of the islet cells, so that there was a deficiency of internal gland secretion, resulting in diabetes. The immediate cause of death was bronchopneumonia, pneumococcus type I. The disappearance of the skin bronzing which was thought to be observed in this case is unusual. Boland and Curran have emphasized the lack of dependability of visible skin changes as a means of diagnosis. Accepting the belief that skin changes are a relatively late manifestation of hemochromatosis, the gradual disappearance of skin pigment as observed clinically and the absence of abnormal skin pigment as demonstrated at necropsy in this case are difficult to explain.

Heredity and the constitution of child. Guyer, M. F., Am. J. Dis. Child. **45:** 601. 1933.

There is no reason to doubt that the amount and quality of the internal secretions in various family strains are as much the expression of hereditary factors as are many other individual characteristics. The hereditary aspect of these glands is likely to be overlooked because they are also subject to environmental modifications. The causes lying back of certain freakish types of development are really based upon genetic factors which affect these glands.
—M. B. G.

The influence of the endocrine glands on the development and maintenance of experimental cancer (Über den Einfluss der endokrinen Drüsen auf das Entstehen und Verhalten der experimentellen Krebserkrankungen). Karnicki, W., Ztschr. f. Krebsforsch. **35:** 523. 1932.

The author reports the results of glandular extirpation and implantation on the development of tar-cancer on the ear of the young, adult rabbit. Five control and five experimental animals were used in each series. Three days after removal of the various glands the inner side of the animal's ear was painted with tar 2 times a week. The control animals developed cancer nodules on an average of 90-115 days after the first application, except on the testicular control group which first developed their cancer in 50-70 days. The average time for development of tar-cancer was 28 days after thymus extirpa-

tion, 33 days after thyro-parathyroidectomy, 36 days after castration, 145 days after unilateral adrenalectomy and 35 days after thymus extirpation plus castration; after a single thymus and testicular implantation the tar-cancer developed on the average in 205 days. The author does not state whether or not the control series were subjected to similar operative procedures except for the actual extirpation of the organ. Genealogy of the rabbits is not mentioned. A brief description of the operative procedures is included. A final series was studied. Rabbits which had had their thymus and testicles removed were given, every 2 days, 1 cc. of a 20% solution of thymo-testicular extract "Klawe," after they had developed large tar-cancers. The injected animals began to show a marked regression of their cancer after 2 injections and in general an arrested growth over a period of 5 months.—R. A. Phillips.

Hormones in cancer; the effect of glandular extirpation upon resistance to tumor tissue grafts. Maxwell, L. C. and F. Bischoff, J. Pharmacol. & Exper. Therap. **46**: 59. 1932.

Tumor resistant rats (8-18 per series with an equal number of controls) were inoculated with R 10 sarcoma after castration, splenectomy, adrenalectomy, and thyroparathyroidectomy. The negative results indicate that these glands are not concerned in the so-called "immunity," or resistance mechanism. Synthalin in sub-lethal daily doses failed to influence the negative response of tumor resistant rats. Massive roentgen radiation over the pituitary region (remainder of body shielded with lead) failed to effect any "takes" in tumor-resistant rats.—R. A. Phillips.

The relation of the thyroid and the hypophysis to the molting process in the lizard, Hemidactylus brookii. Noble, G. K. and H. T. Bradley, Biol. Bull. **64**: 289. 1933.

Either thyroidectomy or hypophysectomy lengthens the period between molts in the lizard, Hemidactylus brookii, but neither operation entirely prevents molting. Thyroidectomy does not delay the appearance of the molt immediately following the operation but affects all later molts. If 6 or fewer follicles remain after thyroidectomy, the effect is the same as complete thyroidectomy. Injections of thyroxine, 1 to 10,000 and later 1 to 30,000, given intramuscularly to thyroidectomized lizards on alternate days, bring a return of the molt to its normal periodicity. However, neither injections of thyroxine nor implantations of fresh lizard thyroid increase the frequency of molt in the intact lizard. Completely hypophysectomized Hemidactylus brookii turn a pale grey and remain this color permanently under varying environmental conditions. Lizards with fragments of the pars intermedia remaining turn a slightly dark tone under conditions where the controls are very dark grey. Removal of the pars anterior of the pituitary alone has the same effect on delaying the molt as removal of the whole gland. The lengthening of the interval between molts may be due to a lowering of the metabolic rate of the lizard and not to any direct action of either the anterior pituitary or the thyroid on the molt mechanism.—G. K. Noble.

The interrelation of a gonotropic hormone and vitamn A. Aberle, S. B. D., Am. J. Physiol. **106**: 267. 1933.

Female rats suffering from avitaminosis of A failed to respond to the injection of a gonotropic hormone. Control animals kept under identical experimental conditions except for the addition of vitamin A to the diet showed the characteristic response. The gonotropic hormone was extracted from human placenta and was standardized on rats and mice. The hormone produced vaginal mucous cells similar to those found in rats and mice during pregnancy. A total of 25 rats commenced the experiment. All the animals were from mothers on a vitamin A low ration. Twelve female rats were given a diet deficient in vitamin A. At a mean age of 59.6 days after cornified vaginal cells had become established, they were ovariectomized. Ten control animals were ovariectomized at a mean age of 47.6 days. After ovariectomy the gonotropic hormone was given in four series of injections. The amount of hormone injected varied from the standardized dose to twice the amount found necessary to produce the characteristic response in the controls. Some animals were sacrificed after each injection in order to study histological sections of the vaginas. Others were allowed to live and the smears were examined

several times a day. Mitotic figures were found in the cells of the vaginas of the injected animals on the vitamin A free diet. The number of mitotic figures compared well with the number of mitotic figures found in the vaginas of the control rats. This shows that the vaginal cells of the animals on the A deficient diet were capable of proliferation. However, no mucous cells appeared in the vaginas of animals suffering from avitaminosis of A. The vaginal cells of the animals kept on the A-deficient diet remained cornified throughout the experiment regardless of the amount of hormone they received. In every control animal characteristic mucous cells were produced in the vaginas as a result of the injections of hormone. In this experiment avitaminosis of A was responsible for preventing the characteristic action of a gonotropic hormone.
—Author's Abst.

The effect of gonadectomy on the adrenal, thyroid and pituitary glands. Anderson, Dorothy and H. S. Kennedy, J. Physiol. **79:** 1. 1933.

An extensive review of the literature precedes the presentation of experimental data. Gonadectomy was performed on rats at 21-22 days and at 80-81 days, and the animals sacrificed at periods ranging from 1 to 9 weeks. In 46 male rats before maturity, the operation did not result in any significant differences in adrenal weights in 1 to 3 weeks. In 9 weeks the adrenals were hypertrophied, contained more lipoid and the histological appearance was that of immature animals. In 12 immature female rats, there was no difference in the adrenals at 1 week and at 9 weeks. The weights of the adrenals approximated those of 10 controls in dioestrus, but were heavier than those of corresponding males. Gonadectomy of males after maturity resulted in no significant differences in the adrenals in 8 weeks. In mature females, the operation resulted in 1 week in adrenal hypertrophy comparable to that at oestrus and above that at dioestrus. In 3 weeks there was adrenal atrophy only in those animals killed in early summer. At longer intervals the atrophy was still more marked. Alterations in size is largely due to changes in the cortex. In each series the thyroid weight tended to decrease, with characteristic histological changes. In male rats, both mature and immature, there was definite hypertrophy of the pituitary. In females, pituitary weight was comparable to that in controls at oestrus, but greater than in gonadectomized males.—C. I. R.

Effect of folliculin on adult ovary (Acción de la foliculina sobre el ovario adulto). Bialet-Laprida, Z., Rev. Soc. argent. de biol. **9:** 131. 1933.

Normal female adult rats (10) were injected subcutaneously daily with 2 R.U. of folliculin for 30 to 35 days. They were killed on the 60th day. The ovaries weighed less than those of the 10 controls (28 and 49 mg., respectively, or 1 mg. of ovary for 2.5 gm. and 4.2 gm. body weight). Mature follicles were seen in the injected animals, but few or no corpora lutea were seen. Atretic and cystic follicles were common. The controls had normal ovaries. After the end of the folliculin treatment the animals remained in dioestrus for 25 days.—J. T. L.

Effect of folliculin on development of ovary (Acción de la foliculina sobre el desarrollo del ovario). Bialet-Laprida, Z., Rev. Soc. argent. de biol. **9:** 123. 1933.

Young female rats (age 17-21 days) were given daily subcutaneous injections of 2 R.U. folliculin, for 54-62 days. At the end of this time their average body weight was 77 gm., while that of the controls was 93 gm. The average ovarian weight was 26 and 42 mg., respectively, so that the treated animals had a smaller amount of ovary per unit of body weight. The microscopic aspect of the ovaries was that of infantile glands. There were no mature follicles nor corpora lutea present in the experimental animals but both were found in the controls. In another series treatment was followed until the animals weighed 120 gm. Here again small ovaries were found, the average weight was 15.8 mg. and that of normal controls was 41 mg. However, in 2 of 5 animals corpora lutea were found. Prolongation of the treatment until the animals weighed 150 gm. resulted in the ovaries being smaller than those of controls but corpora lutea were seen in 4 of 5 animals. After the injection of 5 R.U. daily the inhibition of ovarian growth was even more pronounced.
—J. T. L.

Concerning a case of masculine pseudo-hermaphroditism (Über einen Fall von Pseudohermaphroditismus Masculin). Cadiz, R. and A. Lipschütz, Arch. f. Gynäk. **153.** 593. 1933.

The authors describe the case of a woman 22 years of age, who had never menstruated but whose general habits and emotions, as well as her physical features, were pronouncedly feminine. A thorough medical examination revealed that ovaries, tubes and uterus were missing, and the female genitalia infantile, while two testis-like structures were present. The case was diagnosed as masculine hermaphroditism. The patient was operated upon and the testes were removed. They had the general appearance and consistency of normal male testes, but were somewhat smaller in size. Several photographs of the patient are shown, and numerous cross sections of the testes, seminal vesicles, and epididymis are presented to show that typical interstitial tissue and cells and spermatocytes were present, but no sign of ovary tissue. The authors offer this case as further experimental evidence against the theory of the secretion of sex-specific hormones in the gonads. They conclude that not only did the testes in this case fail to secret male hormone, but very probably were secreting female hormone.—E. B. Womack.

The influence of the corpus luteum on the maternal instinct; experimental researches (L'influenza del corpo luteo sull' impulso materno. Ricerche sperimentali). Cocchi, A., Riv. sper. di freniat. **56:** 24. 1932. Abst., Psychol. Abst., **7:** 4364.

According to the author's experimental findings the corpus luteum of the cow, dried between 45° and 50°, contains a principle capable of inducing a delay of 30-32 days in the appearance of maternal instinct phenomena in birds, if it is absorbed in a given quantity. These findings, supplemented by autopsy examinations, lead to the conclusion that in birds the corpus luteum has biological properties analogous to those of ovarian substance in stimulating the glands of the genetic groups and depressing those of the thyroid-adrenal-pituitary group.

Folliculin abortions in rabbits (Sur l'avortement folliculinique chez la lapine). Courrier, R. and R. Kehl, Compt. rend. Soc. de biol. **112:** 675. 1933.

Doses of folliculin, which did not produce abortion on the 5th or 6th day of pregnancy, did cause it when given on the 12th or 13th day. This is contrary to the usual observation that resistance to folliculin rises as pregnancy advances.—J. C. D.

Further work on pregnancy in rabbits (Nouvelles recherches sur la gestation chez la lapine). Courrier, R. and R. Kehl, Compt. rend. Soc. de biol. **112:** 940. 1933.

Rabbits (number not given) received 10 to 15 units of folliculin on the 21-23 day of pregnancy. This was to sensitize them to corpus luteum extract (progestin) which does not act unless folliculin has been injected previously. The corpora lutea were than removed and progestin injections substituted. In those animals, which did not abort immediately from shock, the pregnancy continued normally.—J. C. D.

Investigations of corpus luteum hormone (Untersuchungen über das Corpus luteum-Hormon). Ehrhardt, K. and W. Weigel, Endokrinologie, **13:** 225. 1933.

In an attempt to find new sources of corpus luteum hormone (progestin) the authors assayed various materials by Clauberg test (infantile rabbit) and by Corner-Allen test (spayed rabbit). A series of eight implantations of human corpora lutea (5 premenstrual, 3 gravid); a series of ten ether-extracted urine assays (premenstrual, gravid, mole and chorioepithelioma); a series of ten infra-red and ultraviolet irradiated placentae, corpora lutea, and normal urine, and a series of twenty plants, juices and ether-extracts, were uniformly negative. Treatment of progestin (Luteohormon, Schering Kahlbaum, A. G.) with Röentgen, ultraviolet, and infra-red rays, with trypsin, pepsin and liquid air did not influence the potency of the extract except in the case of trypsin, which easily destroyed the activity.—M. C. Shelesnyak.

Hormones of posterior lobe of hypophysis and pregnancy toxicoses (Hypophysenhinterlappenhormon und Schwangerschaftstoxikosen). Fauvet, E., Klin. Wchnschr. **10:** 2125. 1931.

The author discusses the experimental results of many investigators and concludes that hydrops gravidarum, pregnancy nephropathia and eclampsia are interrelated. These disturbances occur only during pregnancy and are termed as pregnancy toxicosis. The anatomopathologic changes characteristic of these diseases are due to excess production of posterior pitutary hormone because these conditions can be produced in experimental animals by injecting posterior pituitary lobe extract. The author presents comparative experiments between the hypophysis and the new fraction preparations Tonephin and Orasthin. Tonephin responded in the same manner as hypophysis posterior lobe extract. Until now, the melanophore reaction has not revealed all the effective hormones secreted by the posterior pituitary lobe and in conclusion there is no other available proof than that of the melanophoren reaction to determine and illustrate the increased production of the posterior pituitary lobe hormones in normal pregnancies as well as in pregnancy toxicoses. Experiments seem to emphasize the organic need of hormones from the hypothalmus found in posterior pituitary lobe regardless of whether it functions or not. Stroganoff's method of treatment to prevent pregnancy toxicosis is an indirect proof. It is based on the pharmacologic law that the hormone produced by the posterior pituitary lobe which causes pregnancy toxicosis can be reversed by chloroform anesthesia.—B. Parvey.

Pathologic physiology of teratoma testis. Ferguson, R. S., J. A. M. A., **101:** 1933. 1933. Abst., A. M. A.

The author enumerates the factors determining the quantitative excretion of prolan A in the urine in 117 cases of teratoma testis. It is shown that the excretion of prolan A is determined by the embryonal character of the tumor, the extent of the disease and the effect of treatment. The effect of recurrence and metastasis on the excretion of prolan A in cases of teratoma testis is described. The structural and physiologic changes in the prostate, vesicles, testes and pituitary body of the tumor host are enumerated. The significance of the foregoing observations is discussed.

Oxytocic factors in blood of pregnant women (Investigación de sustancias ocitócicas en la sangre de mujer embarazada). Figueroa-Casas, P., Rev. Soc. argent. de biol. **9:** 175. 1933.

Citrated plasma from women at the end of pregnancy was tested for oxytocic substances by means of the isolated uterus from virgin guinea-pigs (Burn and Dale's method). Of 32 plasmas 78% were active; 44% of plasmas from non-pregnant women (16 cases) and 42% from women in labor (48 cases) were also active. It is concluded that the method does not show that an oxytocic factor in the blood is the cause of onset of labor.—J. T. L.

Comparative studies of gonad-stimulating hormones; effects of prolonged injections in immature rats. Fluhmann, C. F., Am. J. Physiol., **106:** 238. 1933.

The changes resulting from the daily administration to immature rats of acid extracts prepared from human pregnancy blood and from sheep anterior pituitary glands for periods of from 5 to 20 days showed marked differences. The pregnancy-blood extract had a cumulative effect on the ovaries, which progressively increased in weight as the period of injection was prolonged. The daily injection of sheep anterior pituitary extract in such doses that the ovaries increased from 100 to 500% in weight in the first 5 days, failed to produce any further marked increase in ovarian weight when the period of administration was prolonged to from 10 to 20 days. However, the ovaries showed very great increases in weight when much larger daily doses were employed for 15 or 20 days. Significant differences were noted in the histologic picture of the ovaries of the rats given pregnancy-blood extract from those receiving the sheep anterior hypophyseal preparation. The sheep anterior lobe extract produced increases of from 60 to 80% in the weight of the adrenals in 20 days, whereas the pregnancy-blood extract only induced a 30% increase.—Author's Abst.

Experimental cryptorchidism in guinea pigs (A propos de la cryptorchidie expérimentale chez le Cobaye). Foncin, A. R., Compt. rend. Soc. de biol. **112:** 827. 1933.

In 50 guinea pigs degeneration of the seminiferous tubules followed simple closure of the inguinal canal, so that the testes were retained in the abdomen. This disagrees with the report of other workers who failed to get degeneration when the testes were held in the abdomen by direct suturing. It is suggested that the presence of the sutures produced sufficient congestion to maintain a circulation, which preserved the seminiferous tubules for a considerable period and this explains the discrepancy in results.—J. C. D.

On the mechanism of ovulation in the rabbit; quantitative observations on the action of extracts of urine of pregnancy. Friedman, M. H., J. Pharmacol. & Exper. Therap. **45:** 7. 1932.

The ovaries of the post-partum rabbit respond with great regularity to a minimal effective dose of extract when such dose is calculated on the basis of body weight. For the extract in question (Antuitrin) the minimal effective dose is about 1 rat unit per kilo of rabbit. The effects of repeated subminimal doses are not additive, so that two subminimal doses, each representing 0.7 minimal effective dose, may be injected within the space of 12 to 24 hours without producing either ovulation or luteinization. Yet, with repeated subminimal doses injected daily for three days luteinization may be produced without ovulation, so that luteinization of the rabbit follicle can be produced by the injection of an extract at a rate below that which is required to provoke ovulation. The theoretical significance of these results is discussed. Because of the regularity of response, it is suggested that the female rabbit be given a trial in the assay of gonad-stimulating extracts.—Author's Abst.

On the absorption, when given by mouth, of folliculin and its dihydrogenated derivative (Sur l'absorption par la voie buccale de la folliculine et de son dérivé dihydrogéné). Girard, A., G. Sandulesco and A. Fridenson, Compt. rend. Soc. de biol. **112:** 964. 1933.

Dihydro-folliculin was given by mouth to spayed rats. In relatively small doses it stimulated a return of oestrus.—J. C. D.

Pelvic (rectal) palpation of the female monkey, with special reference to the ascertainment of ovulation time. Hartman, C. G., Am. J. Obst. & Gynec. **26:** 600. 1933.

Over 100 precisely determined cases of ovulation in the monkey occurred almost altogether on the tenth to the fifteenth days, a few on other days. An analysis of 53 cases, in which ovulation was recorded in completed cycles, shows that the preovulatory interval is relatively constant and that the variations in total cycle length parallel and are due almost altogether to variations in the length of the postovulatory interval.—Author's Summary.

On the absorption and elimination of folliculin in man (Über die Aufnahme- und Ausscheidungsverhältnisse des Follikulins beim Menschen). Kemp, T. and K. Pedersen-Bjergaard, Endokrinologie, **13:** 156. 1933.

In normal adult males less than ten M.U. of folliculin was found per liter of urine and less than 70 M.U. per day were eliminated in the feces. In two women near the end of pregnancy the feces contained 3,000 to 7,000 M.U. per day. After per oral administration of single large doses of folliculin to men about 6% was recovered in the urine. After subcutaneous administration of similar large doses about 3% was recovered in urine and only slight amounts in the feces. In women near the end of pregnancy the blood contained only 5 to 8% of folliculin contained in the same quantity of urine. Folliculin was found to be equally distributed in blood cells and plasma.—M. O. L.

The relations between the gravid uterus and the corpus luteum in rabbits during the latter half of pregnancy (Sur les relations entre l'utérus gravide et le corps jaune au cours de la deuxième partie de la grossesse chez la lapine). Klein, M., Compt. rend. Soc. de biol. **112:** 819. 1933.

In pseudo-pregnancy in rabbits, the corpus luteum lasts two weeks, in true pregnancy a month, the full period of gestation. To determine whether this

persistence depended directly on the pregnant uterus, rabbits were operated on so that one horn of the uterus was closed and, therefore, remained sterile. The animals had the pregnant horn of the uterus removed at the end of the first two weeks of pregnancy. A week later the sterile horn was removed. The mucous membrane was examined histologically and the musculature physiologically. Both tests showed that the corpus luteum had ceased to secrete. The corpus luteum, therefore, remains active after the fourteenth day only in the presence of a pregnant uterus.—J. C. D.

Treatment of hemorrhages of ovarian origin by means of hormone of corpus luteum (Beiträge zur Behandlung Ovariell bedingter Blutungen mit dem Hormon des Corpus luteum). Knab, F., Zentralbl. f. Gynäk. **57:** 987. 1933.

The author reviews many investigations of the normal relationship between the uterine function and ovarian activities responsible for the present knowledge of ovarian activity by means of ovarian hormone experimentation. These investigators were able to determine and illustrate the causes of the pathologic changes produced in the endometrium due to a disturbed ovarian activity either to an overproduction or underproduction of ovarian hormone, and at the same time an attempt was made to treat uterine hemorrhage of ovarian origin with "Sistomensin." Since it has been demonstrated that the ovarian hormone consisted of two distinct entities which were successfully separated by Allen and Corner, namely, folliculin and corpus luteum hormones, each having a specific action on the endometrium, the author abandoned the use of the former therapy, and claimed to have discovered a worthy substance in the corpus luteum extract which has a hemostyptic effect on uterine bleeding; (a preparation under the name, Luteogon, prepared from the yellow bodies of pregnant cows into ampules of one or two rabbit units). The author presents a series of uterine hemorrhage cases of ovarian origin and by the injection of two rabbit units of Luteogon intra-muscularly for 3 consecutive days, the hemorrhage was controlled and invariably a normal menstrual cycle was re-established. On the basis of the established theory that premature disappearance of the corpus luteum in pregnancy will cause abortion, the author used Luteogon therapy in cases of habitual and threatening abortions in the early months of pregnancy with gratifying success.—B. Parvey.

Masculinization in guinea pigs by partial resection of the ovary (Masculinisation par résection partielle de l'ovaire chez le cobaye). Lipschütz, A., Compt. rend. Soc. de biol. **112:** 1272. 1933.

In 20 guinea pigs, one ovary was entirely removed and the surface of the other stripped off, leaving only the hilus. Six of these showed masculinization. There were alterations in the external genitalia, with normal or overdevelopment of the uterus and vagina, such as follow treatment with the testicular hormone. In two cases, peculiar large cells appeared in the tubules of the hilus.—J. C. D.

The experimental production of sexual characteristics in mammals (Über experimentelle Fixierung von Geschlechtsmerkmalen beim Säugetier). Lipschütz, A., Virchow's Arch. f. path. Anat. **276:** 665. 1930.

Observations on over 100 castrated guinea pigs revealed that the hypertrophy of the breast tissue after implanting bits of ovarian tissue into the kidney lasts long after the ovarian tissue has been destroyed. Included is a discussion of the author's previous work in this field.—R. A. Phillips.

The reactivity and activity of the human uterus at various stages of pregnancy and parturition. Robson, J. M., J. Physiol. **79:** 83. 1933.

Human uterus material removed at operations was used. Graphs were made of the contractions of uterine strips and the responses to pituitrin, pitocin and pitressin recorded for varying stages of pregnancy. There was generally progressively increased sensitivity to oxytocin, ergotoxin and histamine as pregnancy progressed. The degree of rhythmic activity was not correlated with the stage of pregnancy nor with sensitivity to oxytocin.—C. I. R.

A new pregnancy test; the Friedmann reaction on the blood plasma (Sobre una nueva reacción hormonal del embarzo. La reacción de Friedman en el plasma sanguíneo). Schwarcz, R., Semana. med. **1:** 1761. 1933.

Plasma was obtained from citrated blood. The Friedmann method was used with this plasma after detoxification with ether. In 12 cases tested results identical with those of urine were obtained.—A. E. Meyer.

The use of folliculin in involutional states. Sevringhaus, E. L., Am. J. Obst. & Gynec., **25:** 361. 1933.

In 32 women with menopausal symptoms a psychotic picture was present in 17; paresthesias in 16 and insomnia in 19 indicate the nervous disturbances. Of the group 6 had artificial climacteric. The use of simple psychotherapeutic procedures plus small doses of folliculin daily or oftener was found very helpful as had been previously reported for other types of menopausal disturbance. Disadvantages of large doses are pointed out.—Author's Abst.

Effect of hypophysectomy upon pregnancy and lactation in mice. Selye, H., J. B. Collip, and D. L. Thomson, Proc. Soc. Exper. Biol. & Med. **31:** 82. 1933.

Mice were hypophysectomized by a parapharyngeal operation. When the pituitary was removed on the second or fourth day after parturition in 6 mice milk secretion promptly failed.—M. O. L.

Production of endometrial growth in castrated women; minimum dosage of theelin that is required. Werner, A. A. and W. D. Collier, J. A. M. A. **101:** 1466. 1933. Abst., A. M. A.

The authors noted in a previous experiment in which large doses of theelin were given to five castrated women, four of whom had their uteri intact, with the production of certain definite results. It was found that massive dosage is not necessary to produce endometrial growth but that small repeated doses, long continued, produce growth which is roughly proportional to the amount and duration of the theelin injections. In the original experiment endometrial growth was produced by the fourteenth day, at which time 2,800 rat units of theelin had been injected. In one patient endometrial growth developed at the end of 28 days, as a result of having had 2,800 rat units of theelin administered, and one showed endometrial growth at the end of 56 days, at which time she had had a total of 2,800 rat units injected. The authors feel that 2,800 rat units, whether administered over long periods or over shorter periods, must be considered the minimal clinical dosage. As yet they have not conclusive evidence on the relationship between the quantity administered and the quantity eliminated, or between the length of administration intervals and the quantity eliminated. They call attention to the fact that experiments seem successfully to meet the question that has been often asked whether or not smaller doses might not produce the results actually obtained from the administration of theelin. They are judging the minimal dose by the development of a clearly recognizable and accepted criterion. Dosages, therefore, given previous to the development of this criterion, namely, the production of endometrial growth, must be considered clinically subminimal dosages. Uterine bleeding, which occurred frequently, did not bear a definite relation to the degree of endometrial growth. Two patients who received 100 rat units of theelin every other day, showed endometrial growth and had uterine bleeding; in fact, one bled cyclically on four occasions in a normal manner. The breasts and genital tracts of all patients showed enlargement and greatly increased activity. Relief from the subjective symptoms that follow castration was had in all patients, and libido was markedly increased in nine of the ten patients who were treated.

Five hundred and nineteen Voge bromine tests of urine for pregnancy. Young, A. M., J. Lab. & Clin. Med. **19:** 153. 1933.

Examination of 519 specimens has shown that the Voge bromine test is far from a satisfactory test for the diagnosis or exclusion of pregnancy. Positive results were obtained in but 63% of the pregnancy urines and negative results in only 84% of the nonpregnancy urines.—Author's Summary.

Some hermaphrodites I have met. Young, H. H., New England J. Med. **209:** 370. 1933.

Fourteen cases of varying degrees of intersexuality from the author's records are described. One is that of a true hermaphrodite, the twelfth authenticated case on record. He was apparently a normal male, nearly six feet tall, strong, and athletic. Operation revealed a left ovary with Graafian follicles, uterus and tube. The scrotum contained a right testis, as proved by section. The ovary was removed and the testis was retained. He married and lived as a normal male.—J. C. D.

The use of pituitary extract in obstetrics. Alden, C. R., New England J. Med. **209:** 1211. 1933.

This paper covers the therapeutic use of posterior lobe extract and summarizes current practice but does not touch on its endocrine aspects.—J. C. D.

Effect of anterior pituitary extract and basal metabolism (Acción del extracto de lopbulo anterior de la hipófisis sobre el metabolismo básico). Artundo, A. and L. A. Solari, Rev. Soc. argent. de biol. **9:** 143. 1933.

Toads (B. arenarum) were enclosed in hermetically closed glass jars of 10 U. capacity with a little water and maintained at 18-20° C. in a dark, quiet room. The oxygen consumption was determined every 24 hours. It was found to be 38-80 cc. per kg. per hour. No significant difference was seen after daily subcutaneous implantation of 3 anterior pituitary lobes during 3-4 days, in normal and thyroidectomized males and females after ovulation. Females implanted before ovulation had a marked rise which is attributed to movements caused by the expulsion of ova provoked by the implantation. Dogs (5) received 1-7 cc. per kg. of weight of anterior pituitary extract (Evans and Simpson) intraperitoneally daily for 6-14 days. The basal metabolism increased considerably (20% to 128%). With the larger doses and more prolonged treatment the increase was greater. It was evident after 3-4 days and lasted for 4-13 days after suspension of the injections. Pulmonary ventilation increased, perhaps being due in part to increase in temperature which was from 0.5° to 2° C. above the initial temperature. The respiratory quotient was not modified. Increase in pulse rate was always seen in relation to increase in metabolism. The body weight was slightly increased.—J. T. L.

The induction of precocious maturity in the reproductive tract of recently metamorphosed female salamanders by an extract of the mammalian hypophysis. Burns, R. K. and A. Buyse, Anat. Rec. **58:** 37. 1933.

When an extract of the mammalian hypophysis is administered continuously to immature female salamanders (Amblystoma tigrinum Green) immediately after metamorphosis, precocious maturation of the reproductive tract occurs to an extraordinary extent. The ovaries without exception become greatly enlarged, and develop numbers of practically mature eggs, although there is considerable individual variation. These eggs are of normal size and contain the usual amount of yolk and pigment, but nuclear maturation and ovulation had not occurred when the experiment was terminated. There is remarkable hypertrophy of the oviduct correlated with the development which has occurred in the ovary. Yolk formation is necessary before marked development of the oviduct begins. These observations are based on six experimental cases and five controls, chosen for uniformity of size from animals reared in the laboratory from one clutch of eggs. The results are compared with a similar series of experiments upon larval animals, and with the somewhat different findings in mammals. The results are likewise of interest as another example of the effectiveness of a mammalian hormone in producing an homologous effect in amphibians. The failure of ovulation to occur indicates that the maturity induced falls somewhat short of the normal functional state; since the same extract readily induces ovulation in adult females. Possibly a slightly prolonged treatment would have produced ovulation.—R. H. Burns.

The histological origin of the hormones of the posterior lobe; "Intermedian" (Sur l'origine histologique des hormones posthypophysaires. L'intermedine). Collin, R., Compt. rend. Soc. de biol. **112:** 1351. 1933.

The secretion, which dilates the melanophores, is termed "intermedian." It is attributed to the pars intermedia. In birds, there is no pars intermedia.

In man and certain other animals, the cells in the adult pars intermedia resemble those of the anterior. There is reason to believe, therefore, that not only the intermediate but also the anterior lobe may elaborate "intermedian."
—J. C. D.

The anterior pituitary sex hormone in relation to the prolongation of estrous cycles and the production of a refractory condition of theelin. Emery, F. E., Anat. Rec. **57:** 315. 1933.

Some chronic effects of pituitary treatment have been studied in more than 70 albino rats. These data are compared to a similar number of normal and other control rats. Daily vaginal smears were taken of normals and of rats that had received the anterior pituitary sex hormone either as implants or extracts over a period of 2 days. The mean length of the estrous cycles varied from month to month but remained longer than normal for a period of more than a year in the rats that were brought to sexual maturity at 26 days of age by the anterior pituitary sex hormone. The longer cycles in the experimental group were due to longer diestrous periods. When implants or potent extracts of the pituitary are given to immature rats the first estrus occurs in 2 to 4 days. This is followed by a diestrous period of several weeks' duration. During this diestrous period the reproductive tract is refractory and will respond to injections of theelin in dosages as high as 100 R.U. Ovariectomy and hysterectomy had no apparent effect on this inhibition to theelin.
—Author's Abst.

Gumma of the hypophysis and hypothalamus. Fink, E. B., Arch. Path. **15:** 631. 1933.

Report of a case of gumma of the hypophysis in a 34-year-old woman. Clinically, the symptoms were typical of cerebral vascular lues with basilar meningitis involving the left oculomotor nerve and optic chiasm. Anatomically, the hypophysis and hypothalamus were destroyed by a huge gumma. Less than 30 cases of gumma of the hypophysis have been reported, five of which also involved the diencephalon. In the presence of signs of cerebral syphilis, the occurrence of hypopituitary symptoms justifies the diagnosis of syphilis of the hypophysis. Tremor, weakness of the extremities, unstable gait, atrophy of the extremities and hypertonia indicate injury to the thalamus. Polyuria is a sign of involvement of the stalk or of the tuber cinereum. Syphilis of the hypophysis cannot cause acromegaly, because the syphilitic process produces a destructive lesion. Acromegaly is due to hyperfunction of the hypophysis, the result of hyperplasia or tumor.—Author's Abst.

Relation between the anterior lobe of the hypophysis and the gonads (Über die Beziehungen zwischen Hypophysenvorderlappen und Kiemdrüsen). Hohlweg, W. and M. Dohrn, Klin. Wchnschr. **11:** 233. 1932.

In immature castrated female rats daily doses of 1/30 R.E. follicular hormone ("Progynon") prevents the castration changes in the hypophysis. About 12 times this dose is necessary in the male. In sexually mature females a daily dose of 5 to 6 R.E. is necessary to prevent the castration changes. The treatment must be continued for at least three weeks both in infantile and mature rats. Larger doses for a shorter period will not obliterate castration changes in the hypophysis. The results of Evans and Simpson on the increased activity of the anterior lobe of the hypophysis after castration were corroborated. The hypophyses from mature normal female rats, from castrated females treated daily with follicular hormone, and from untreated castrated females, were transplanted into immature female rats. Only in the case of the hypophyses from untreated castrated female rats is there precocious growth of the genital organs and appearance of follicles and corpora lutea in the ovaries. The follicular hormone apparently maintained the hypophysis of the treated castrated female rats in a normal physiological state. When an ovary from a normal rat of the same age is implanted into an infantile female rat three weeks after castration, the vagina is caused to open. The recovered implant showed large follicles and corpora lutea. If the ovary is implanted on the day of castration, no such changes occur. Only a single oestrual cycle appeared, after which the animal returned to the normal state for its age. Apparently the gonadotropic function of the anterior lobe of the hypophysis is kept within physiological limits by the checking action of the sex-gland hormones. Details as to the number of animals involved are not given.—A. T. R.

Effect of anterior pituitary extract and specific dynamic action in thyroidectomized and hypophysectomized-thyroidectomized dogs (Extracto antero-hipofisario y acción específica dinámica en perro tiroprivos y tirohipofisoprivos). Houssay, B. A. and A. Artundo, Rev. Soc. argent. de biol. **9:** 168. 1933.

Respiratory metabolism was determined in dogs in basal conditions and 2 and 5 hours after ingestion of 300 gm. meat. In normal animals (5) the increase over basal was 215 and 220 calories (calculated for 24 hours) at 2 and 5 hours after the protein meal. Thyroidectomized dogs (6) had a smaller rise after protein ingestion (161 and 179 calories, 22% less than in normals). Thyroidectomized-hypophysectomized dogs (7) also had a small increase (133 and 150 calories, 35% less than normal). Treatment with an alkaline anterior pituitary extract (Evans and Simpson) did not significantly alter the metabolic response to protein feeding.—J. T. L.

Effect of anterior pituitary lobe extract on basal metabolism of hypophysectomized and thyroidectomized dogs (Acción del extracto antero-hipofisario sobre el metabolismo básico de hipofisoprivos y tiroprivos). Houssay, B. A. and A. Artundo, Rev. Soc. argent. de biol. **9:** 161. 1933.

Normal dogs were injected intraperitoneally with 10 cc. anterior pituitary extract (Evans and Simpson) for 6 days. This dosage corresponded to 0.3 gm. fresh gland. On the 2 days following the end of treatment 4 of 5 dogs showed an increase in basal metabolism. All had an increase in pulse rate (22-55 beats p.m.), in respiration and temperature. Hypophysectomized dogs also showed an increase in basal metabolism, pulse rate, respiration and temperature similar to that of the normal animals. Thyroidectomized dogs showed a slight increase in metabolism in one case and a decrease in 3 cases after treatment; the increase in pulse and respiratory rate and in temperature was considerably less than in normal controls. Thyroidectomized-hypophysectomized dogs (4) responded to treatment in the same manner as did the thyroidectomized animals, the difference from normal being more accentuated. It is concluded that the metabolic activity of the extract is performed by stimulation of the thyroid.—J. T. L.

The influence of hormonal substances on the function of the anterior lobe of the pituitary and the practical importance of this (Die Beeinflussung der Hypophysenvorderlappenfunktion durch hormonale Substanzen und deren praktische Bedeutung). Kraul, L., Arch. f. Gynäk. **148:** 65. 1932.

Various animals were injected as indicated below and then their hypophyses were removed and implanted into 2-week-old mice (litter mates for controls). Five days later the mice were sacrificed and the ovaries studied microscopically. The conclusions were: (1) Injection of folliculin increases the prolan A activity of implanted anterior lobe substance; (2) corpus luteum extract brings forth the prolan B activity in the same fashion; (3) after injections of urine-of-pregnancy the luteinization activity prevails in the implant; (4) adrenaline increases somewhat the development of follicles; (5) placental tissue works in various fashions. Of practical importance is the knowledge, that with the use of the infantile mouse as test-object one must consider the activity of the subject's hypophysis.—R. A. Phillips.

Further studies on the coefficient of luteinization (Nouvelles recherches sur le coefficient de lutéinisation de la préhypophyse). Lipschütz, A., Compt. rend. Soc. de biol. **112:** 1145. 1933.

The power of stimulating the formation of corpora lutea on the part of extracts of the anterior lobe may be expressed quantitatively. The number of milligrams of lutein tissue formed is divided by the number of milligrams of hypophysis administered. The amount of lutein tissue is calculated from serial sections. By this formula the coefficient of luteinization for the hypophysis from an adult female rat is 0.003, from a young female 2.56, and from a spayed adult 1.24.—J. C. D.

Anterior pituitary hormones acting on the ovary and differences in the reactions in different species. Loeb, L., Proc. Soc. Exper. Biol. & Med. **30:** 1335. 1933.

The facts concerning the action of various anterior pituitary preparations on the sex organs can be best explained by the assumption that there are at

least two types of anterior pituitary hormones which act on the ovary, one of which also affects the thyroid gland. Hormone I is responsible for the increase in size of the ovarian follicles and for the maturation processes which take place in the granulosa of follicles. This hormone counteracts the tendency of the granulosa to undergo degeneration, leads to the maturation of the granulosa primarily of the large sized follicles but may also cause beginning or further advanced maturation of the granulosa of medium-sized and even smaller follicles. If no inhibiting mechanisms are at work, the production of large mature follicles leads to ovulation and to the formation of true corpora lutea with the consequences which follow from the functioning of these organs. However, in many cases, the mature follicles do not give rise to ovulation, but an ingrowth of capillaries and of connective tissue cells from the theca interna into the granulosa of such follicles occurs. This is followed by the transformation of the granulosa cells into lutein cells and is often accompanied by an increase in the size of the theca interna cells. In the rat, especially, these latter processes can be readily recognized. A second hormone (II), either performed in the anterior pituitary or originating after removal of the gland from the animal, acts in the opposite manner on the granulosa of the follicles, inhibits the growth or accelerates the degeneration of the granulosa cells in species in which the granulosa cells are of a more labile character. It allows the transformation of theca interna into interstitial gland or pseudolutein tissue and of certain connective tissue cells into lutein-like cells during or following the process of atresia of follicles. Thus, structures are produced which show various kinds of intermediate conditions between atretic follicles and corpora lutea. These effects, the inhibition of the growth of the follicle and of the tendency of the granulosa to undergo maturation, and the production of a hypertrophic type of atresia of follicles, leading to the formation of structures which if they reach a relatively large size may resemble corpora lutea, and the production of only rudimentary interstitial gland, due to the activity of the theca interna and possibly also of certain connective tissue cells, are combined and may therefore probably be attributed to the same pituitary hormone, although the first change may occur without being followed by the second. The hormone acting as stimulator of the thyroid gland can be independent of the follicular growth and maturation hormone I, but it has always been found associated with hormone II. This thyroid effect appears after inoculation of anterior pituitaries relatively rich in hormone I (rat, rabbit, guinea pig) only, if at the same time interstitial gland and other types of lutein-like tissue are produced.—H. Friedman.

The action of the pituitary sex hormone on the testicles after ligature of the vas deferens (L'azione del ormone sessuale ipofisario sui testicoli dopo legature dei deferenti). Lucarelli, G., Sperimentale, Arch. di biol. **87**: 5. 1933.

Guinea pigs were treated with prolan one month after the ligature of the vas deferens. The residue of germinative cells was stimulated to abundant growth and spermatozoa were formed. The interstitial cells also increased and the lipoid content of the tissues was high.—A. E. Meyer.

Hypophysis and blood glutathione (Hipófisis y glutation sanguíneo). Maveroff, H., Rev. Soc. argent. de biol. **9**: 227. 1933.

In 9 hypophysectomized dogs the glutathione in total blood (Braier and Marenzi's method) was the same as in 18 normal controls. Glutathione in cells was 10% lower in the operated animals. Evans and Simpson's alkaline anterior pituitary extract given 6 days intraperitoneally increased the glutathione in the blood corpuscles of 5 of 6 normal dogs, 4 hypophysectomized, 3 thyroidectomized, 2 thyroid-hypophysectomized dogs and 2 dogs with lesion of the tuber cinereum.—J. T. L.

The control of the dermal melanophores in elasmobranch fish. Parker, G. H. and H. Porter, Biol. Bull. **66**: 30. 1934.

The common dogfish, Mustelus canis, has a dark phase and a light one due to the expansion and the contraction of its dermal melanophores. The dark phase is induced by pituitary secretions carried from the pituitary gland to the melanophores by the blood and lymph as described by Lundstrom and Bard. The light phase is induced through the action of contracting nerves,

and is not merely the result of the absence of pituitary secretions. The expanding hormone is water-soluble. The contracting one, if there be such, is apparently not water-soluble. The dogfish is remarkable as the first form to be described in which the cutting of nerves induces a contraction of the melanophores and a consequent lightening of the skin.—Authors' Summary.

The present status of diseases of the hypophysis. Putnam, T. J., New England J. Med. **209:** 486. 1933.

The author reviews briefly the physiology of the pituitary and then points out that pituitrin relieves diabetes insipidus but that this is the only instance where pituitary preparations have up to the present proved of consistent value in pituitary disorders.—J. C. D.

The percentage of the different types of cells in the anterior lobe of the hypophysis in the adult human female. Rasmussen, A. T., Am. J. Path. **2:** 459. 1933.

A differential count was made of the three types of cells found in the anterior lobe of 94 carefully selected and supposedly normal formalin-fixed hypophyses of non-pregnant females 16 to 84 years of age (average 42 years) from cases of sudden or accidental death, and of 25 pregnant females 15 to 39 years of age (average 27 years), using Mallory's connective tissue stain after slight staining with hematoxylin. An average of 214 sample fields and a total of 15,000 cells were counted in each hypophysis. In the non-pregnant the chromophobes averaged nearly 50% of all cells, with a coefficient of variation of 14; the acidophils (alpha cells) averaged 43%, with a coefficient of variation of 19; and the basophils (beta cells) averaged 7%, with a coefficient of variation of 42. Thirty-three women above 50 years of age (average 61 years) had, on an average, 4% more chromophobes, nearly 2% more basophils and 6% fewer acidophils than were found in 61 non-pregnant females under 50 years of age (average 31 years). There is no correlation between body length and any particular type of cell. While there are, on an average, relatively fewer acidophils and more chromophobes in the pregnant women than in the non-pregnant, the differences are too small to be statistically significant. The enlargement of the anterior lobe of the hypophysis during pregnancy is apparently not due to a marked hyperplasia of any one of the three regularly recognized types of cells, nor could a special so-called "pregnancy cell" be identified. When compared with similar data from 100 apparently normal men, women have about 7% more acidophils, 3% less chromophobes and 4% less basophils than men.—Author's Abst.

The indirect endocrine relationship between hypophysis and tuber cinereum (A propos de la neurocrinie hypophyso-tubérienne indirecte). Roussy, G. and M. Mosinger, Compt. rend. Soc. de biol. **112:** 1203. 1933.

Capillaries pass from the hypophysis to the region of the infundibulum. In the vessels under certain conditions, stainable material is seen indicating that hypophyseal secretion reaches the region of the 3rd ventricle in this way. Dogs, cats, and guinea pigs were studied.—J. C. D.

The effect of the growth hormone on body and tail lengths. Rubinstein, H. S. and L. J. Kolodner, Anat. Rec. **58:** 107. 1934.

Seventy-four white rats (Mus norvegicus var. albinus) were divided so that each group contained either male or female test animals and litter mate brothers or sisters as controls. Two sets of controls were used, one remaining uninjected, the other receiving meat extract prepared exactly as the growth hormone. The test animals received daily (except Sunday) intraperitoneal injections of pituitary growth hormone for 22 weeks. After this period all animals were sacrificed and measured. On the basis of these measurements, statistically computed, it was concluded that the growth hormone increased the body and tail lengths of all animals injected. The male responded somewhat less than the female. Animals injected with meat extract showed no significant deviation from the uninjected controls.—Authors' Abst.

On the lack of identity between prolan and the gonadotropic hormone of the anterior lobe of the hypophysis (Sur la non-identité du prolan et de l'hormone gonadotrope préhypophysaire). Schockaert, J. A., Compt. rend. Soc. de biol. **112:** 732. 1933.

One hundred and two immature male rats were divided so that litter mates were injected with alkaline hypophyseal extract, prolan, or were used as controls. After one or two weeks the animals were autopsied and the growth of the testes and the secondary sex organs compared with that of the controls. Prolan produced a very much more rapid growth in the accessory organs than did hypophyseal extract. Size relation between the testes and secondary organs is expressed as an absolute value the "index genocinetiques." In immature drakes and cocks, prolan does not hasten maturity while anterior lobe extract does.—J. C. D.

A cytological study of the anterior pituitary of the rat with special reference to the Golgi apparatus and to cell relationship. Severinghaus, A. E., Anat. Rec. **57:** 149. 1933.

This paper is devoted to a cytological description of the anterior pituitary of the normal and the castrated rat, and will be supplemented with a description of the pituitary in the female in pregnancy and in relation to the sex cycle. Especial emphasis has been placed upon such cytoplasmic structures as the mitochondria and Golgi apparatus and these features have been utilized in the study of cell-relationships within the anterior pituitary. The demonstration of granular mitochondria in both the acidophiles and basophiles similar to acidophilic granules makes it reasonable to assume that the basophilic mitochondria, mistaken for acidophilic granulation, have been the basis for the erroneous transitional stages described between basophilic and acidophilic cells. The supposition that transitions between basophiles and acidophiles do not occur is supported by the fact that these two types of cells have morphologically different Golgi apparati. The chromophobes have a Golgi apparatus which may be either of the acidophilic or basophilic type, a fact which is interpreted as demonstrating a direct relation of the chromophiles to their respective chromophobic progenitors. A study of the Golgi apparatus in the pituitary of the castrate further reveals that the "castration cell" has the typical basophilic type of Golgi, but that it takes no part in the formation of the colloid-like vacuolation of the cytoplasm.—Author's Abst.

On the physiology of puberty; the excretion of anterior pituitary hormone-A in urine (Zur Physiologie der Pubertät. Die Ausscheidung des Hypophysenvorderlappenhormon-A im Urin). Soeken, G., Ztschr. f. Kinderh. **53:** 339. 1932.

The urine of 50 children and infants ranging in age from one to 18 years was tested for the presence of anterior pituitary hormone by the method of Aschheim-Zondek on mice. In 50% a positive anterior pituitary hormone-A reaction was obtained but in not a single instance was the B luteinizing hormone found. One male child with acromegalic appearance and pubertas praecox due to eosinophilic pituitary tumor gave a positive reaction. There was no difference between the sexes. The results do not indicate that there is a greater excretion of anterior pituitary hormone-A in urine in puberty as the percentage of positive reactions in puberty and adolescent periods is not any greater than in childhood. There is an extensive discussion of the subject with reference to the observations of other investigators.—M. B. G.

The clinical significance of pituitrin-hyperglycemia (Zur klinischen Bedeutung der Pituitrin-Hyperglykämie). Aschner, B. and L. Jaso-Roldan, Ztschr. f. klin. Med. **121:** 495. 1932.

The blood sugar values (Hagedorn-Jensen micro-method) were observed in 31 patients before and at 20-minute intervals (for 90 minutes) after the intramuscular injection of 2 cc. "Pituisan." Of the 31 patients 18 were normal, and the remainder included patients with acromegaly, hyperthyroidism, diabetês, Addison's disease or hypogenitalism. The authors conclude that the variations in the blood sugar values are not significant enough to aid in reaching a diagnosis of the condition.—R. A. Phillips.

Modifications of glycemia, blood pressure and pulse after intravenous injection of insulin in subjects with normal carbohydrate exchange (Sulle modificazione della glicemia, della pressione e del polso dopo iniezione endovenosa di insulina in soggetti con normale ricambio idrocarbonato). Battistini, S. and L. Rigoletti, Minerva Med. **1**: 656. 1933. Abst., Chem. Abst. **27**: 3751.

Patients were given 14 units of insulin after fasting 16 hours and glycemia was determined (Folin-Wu) 13 times within one and one-half hours. In 6 normal persons the glycemia fell to an average of 44 mg. per 100 cc. in 20-35 minutes after injection. The ascending phase was longer and irregular. In 5 patients with hypertension the average minimum glycemia was 51 mg. per 100 cc. A patient with malignant hypernephroma and one with acromegaly showed no alteration in glucose tolerance. In a patient with visceral ptosis glycemia fell from 81 mg. to 30 mg. in 15 minutes, rose slightly, then fell to 14 mg. within 45 minutes after injection. Glycemia remained below 20 mg. for about an hour.

Insulin and sugar tolerance in thin people. Blotner, H., Arch. Int. Med. **53**: 153. 1934.

Insulin is now being used widely in the treatment of undernutrition in non-diabetic persons. It appeared of interest to study the effect of insulin on the sugar tolerance of such persons since the drug has been reported to have an appreciable effect on this phase of metabolism. The work reported here was carried on in 25 normal thin patients made to gain weight with insulin according to the following methods: The dextrose tolerance was observed before, during and after the administration of insulin in nine cases, during and after a course of insulin therapy in seven cases and only after insulin had been omitted in nine cases. In the cases studied during a period of treatment with insulin, 10 or 15 units of the drug were taken three times a day for from one to twelve weeks before the test was made, and in the cases studied after insulin was omitted, a period of from three days to two years after the discontinuance of insulin therapy elapsed before the final test was made. A standard dose of 100 gm. of dextrose was employed. This was mixed with 250 cc. of water, flavored with 50 cc. of lemon juice, chilled and ingested after the patient had fasted for at least 14 hours. The concentration of sugar in the blood and urine was determined in specimens taken during fasting and at intervals of one-half, one, two and three hours after the ingestion of the dextrose mixture, the determinations of blood sugar being made on 0.1 cc. samples of venous blood according to the the micromethod of Folin and Malmros. Then while the patients were taking their usual diets during various periods of observation, occasional samples of urine and of blood were collected after various meals and examined for sugar. Three types of curves for sugar tolerance were obtained. In one, the curves for blood sugar were normal, and the urine remained sugar-free during all the periods of observation. In the second, the curves for blood sugar were normal during the various periods of study, but during the period of administration of insulin glycosuria appeared, usually one or two hours after the ingestion of dextrose. In the third type, the curves for blood sugar were normal either before or after the use of insulin, but during the period of treatment with insulin there developed a considerable increase in the concentration of the blood sugar in one-half or one hour after the ingestion of dextrose; this was associated with glycosuria, which usually appeared in one or two hours. The cause of the temporary decrease in tolerance induced by insulin is a matter of speculation. It is suggested that the type of tolerance associated with glycosuria and normal curves for blood sugar is due to a decreased renal threshold and the type associated with glycosuria and hyperglycemia, to either an increased absorption of sugar from the gastrointestinal tract or a temporary suppression of pancreatic function. Regardless of the cause of the glycosuria and hyperglycemia encountered, the finding was of no practical significance, since the sugar tolerance invariably returned to normal shortly after insulin was omitted. Decrease in tolerance to the customary diets employed by these patients while they were taking insulin for the purpose of gaining weight was not observed, even though the diets contained abundant amounts of carbohydrate.—Author's Abst.

Choline and liver fat in diabetic dogs. Best, C. H., G. C. Ferguson and J. M. Hershey, J. Physiol. **79**: 94. 1933.

Fatty infiltration and degeneration of the liver in diabetic dogs was prevented by feeding choline.—C. I. R.

Lactation in diabetes. Chaikoff, I. L. and W. R. Lyons, Am. J. Physiol. **106**: 716. 1933.

Six completely depancreatized dogs that were kept alive by means of insulin and a special diet, and four normal dogs were injected with the lactation hormone obtained from the anterior pituitary gland. The secretion of milk was observed in all normal dogs. Five of the diabetic animals failed to lactate despite the fact that the amount of hormone injected was greater, and the period of its injection much longer than that found necessary to induce lactation in the normal dogs. In a single depancreatized dog lactation followed the administration of the hormone.—Authors' Summary.

The pancreas and the vagi in muscle glycogen restorage after fatigue in cats (Papel del pancreas y del vago en la reconstitución del glucógeno muscular después de la fatiga en el gato). Dambrosi, R. G., Rev. Soc. argent. de biol. **9**: 441. 1933.

In chloralosed cats, tetanization for 15 minutes produced a considerable decrease in muscle glycogen. After 1 hour of complete rest a normal figure was again observed. Immediately after pancreatectomy, muscle glycogen recovery was normal; 24 hours later no glycogen was restored in fatigued muscle during a rest period of 1 hour. Treatment with insulin (3 units per kg.) re-established the normal capacity of the muscle for glycogen restorage. Vagotomy alone or combined with splanchnicotomy did not alter the muscle glycogen restorage in chloralosed cats. Vagotomized cats anaesthetized with ether did not recover their muscle glycogen after fatigue; a slight recovery was seen when artificial respiration was given. Ether anaesthesia alone in normal cats considerably diminished the amount of glycogen restored by muscle after fatigue.—J. T. L.

The pancreas in muscle glycogen recovery after fatigue (Papel del páncreas en la reconstitución del glucógeno muscular después de la fatiga). Dambrosi, R. G., Rev. Soc. argent. de biol. **9**: 430. 1933.

Pancreatectomized dogs 5 and 24 hours after operation had normal muscle glycogen values. Recovery of muscle glycogen after fatigue was normal up to 1 hour following operation. It was incomplete 2-3 hours after pancreatectomy and deficient 4-24 hours after. Recovery was delayed but not suppressed. Examining the muscle several hours after fatigue a greater glycogen content was seen the longer the recovery period lasted. Ether anaesthesia given for operation was not responsible for this result. Incomplete pancreatectomy was not followed by alterations in the muscle glycogen recovery after fatigue. Pancreatectomized dogs treated with insulin had normal muscle glycogen restorage. Insulin (10-15 units) did not produce a super-normal muscle glycogen restorage in normal dogs. A pancreatic graft had the same results as insulin injections in restoring the capacity for glycogen recovery in pancreatectomized dogs. In conclusion it is deduced that insulin secreted by the pancreas is an important factor in maintaining a normal velocity of muscle glycogen restorage.—J. T. L.

The vagi and splanchnic nerves in muscle glycogen restorage in dogs (Influencia de la sección de los vagos y esplácnicos en la recomposición del glucógeno muscular en el perro). Dambrosi, R. G., Rev. Soc. argent. de biol. **9**: 438. 1933.

Vagotomy (2-24-48 hours previously) did not alter the muscle glycogen restorage after fatigue. Section of the splanchnics and extirpation of the lumbar sympathetics practiced several days previously did not alter the normal recovery, and neither did vagotomy combined with lumbar sympathectomy and section of the splanchnics.—J. T. L.

Studies of retinopathies; diabetes mellitus. Gresser, E. B., Am. J. Ophth. **16**: 571. 1933.

In a study of 100 cases of diabetes mellitus, the clinical signs of hypertension, retinal vascular sclerosis, and abnormal urinary elements are correlated, together with age and duration of the diseased state. In group I, 38% sclerosis and hypertensive signs in the vessels were practically uniformly pres-

ent. Associated nephritic lesions were found in 23.5% and benign hypertension in 72% of these. The retinopathy seen in these diabetics did not conform to one clear picture, no entity having been established. The majority showed characteristics of hypertensive retinitis, both vascular and exudative. No relationship was seen between the presence of retinopathy and the severity of diabetes. In group II, 30%, signs of retinal vascular sclerosis without other vascular or retinal changes were present. All in this group were free from renal disease and permanent hyperpiesis was absent. The duration of the diabetic state was not, apparently, a direct factor in the production of retinal pathology. In group III, 32%, no alterations in the retinal vessels or tissues were present. Blood pressure ranges were normal and urinalysis was negative except for sugar.—Author's Abst.

Hyperinsulinism, a definite disease entity; etiology, pathology, symptoms, diagnosis, prognosis and treatment of spontaneous insulogenic hypoglycemia (hyperinsulinism). Harris, S., J. A. M. A. **101:** 1958. 1933. Abst., A. M. A.

The author gives the definition and frequency of hyperinsulinism and states that hunger is the most constant symptom. At least a hundred cases have been reported by American and European clinicians, surgeons and pathologists who have made thorough studies of all phases of hypoglycemia due to the hypersecretion of the islet cells of the pancreas. Sufficient data have accumulated in medical literature to warrant the discussion of hyperinsulinism as a definite disease entity. The author endeavors to outline the etiology, pathology, symptoms, diagnosis and treatment of hyperinsulinism as derived from published reports of many cases and from a study of the disease over a period of ten years.

Neurological manifestations of hypoglycemia. Jordan, W. R., New England J. Med. **209:** 715. 1933.

The author warns against unusual symptoms and dangerous reactions associated with hypoglycemia. He reviews the literature and cites six cases of his own. These showed paresis, hemiplegia, or localized paralysis, which cleared up after the carbohydrate balance had been restored.—J. C. D.

Fat and the diabetic. Joslin, E. P., New England J. Med. **209:** 519. 1933.

Twenty years ago obesity was considered a cause of diabetes. Hereditary influences are now recognized as important and efforts are concentrated on preventing overweight in diabetically predisposed individuals. If both parents are diabetic, all the children will suffer. If one parent is diabetic and the other is from a diabetic family, one-half of the children will be diabetic. If both parents are from diabetic families, but not diabetic themselves, one-fourth of the children will have diabetes. If a healthy individual from a non-diabetic family marries a healthy partner from a diabetic family, none of the children will inherit the tendency. Overeating is an essential factor. Ingestion of excess fat or carbohydrate overtaxes the pancreas. Sudden increase of weight, such as comes with change of occupation or immobilization due to injury, is dangerous. Fat and carbohydrate metabolism are interdependent. If sufficient carbohydrates are fed, large amounts of fat can be ingested without overstorage of it in the liver. Depancreatized dogs can be kept in good health indefinitely, provided pancreas is fed in addition to sufficient diet and adequate insulin injections. The active factor in the pancreas is one of the components of lecithin, betaine a non-toxic oxidation product of choline. Without betaine, insulin therapy results eventually in death associated with a fatty liver. Cholesterol is the indicator used to follow the fat in the blood. With improved diets it has come down to within normal limits in diabetics. If it remains high in a case, the diabetes is not being properly controlled. There are some indications that arteriosclerosis and cataract are associated with excessive blood fat. In the days of unlimited fat in the diabetic diet. 60% died in coma. With the limitation of the caloric value of the diet, this figure fell to 40% and since insulin has been used to 5%. The diets now recommended approximate 140 grams carbohydrate, 70 grams protein, 90 grams fat. Increase in caloric value as for growing children is taken care of by increasing fat and carbohydrate equally. Unless the diet keeps the fat under 230 milligrams per 100 cc. of blood, the case is not under control and the prospect of the immediate and remote consequences is alarming.—J. C. D.

Insulin secretion after radiation of the pancreatic region (L'insulino-sécrétion au cours des irradiations de la région pancréatique). La Barre, J. and P. Lorthioir, Compt. rend. Soc. de biol. **112:** 722. 1933.

The blood from the pancreas of one dog was shunted through the circulation of a decapsulated dog. The pancreatic region of the donor was irradiated. Hypoglycemia of the receptor followed, indicating an increased insulin output from the pancreas of the donor. If the donor is decapsulated before irradiation, there is no increased output of insulin. The hypoglycemia following irradiation of the abdomen depends, therefore, primarily on stimulation of the adrenals, which stimulate the pancreas secondarily. Three examples are given.—J. C. D.

Arteriosclerosis and diabetes mellitus. Lehnherr, E. R., New England J. Med. **208:** 1307. 1933.

Chemical studies were made on aortae from 25 diabetic adults, 25 non-diabetic adults, and 6 non-diabetic children. Pipid, calcium, and phosphorous content were studied and the results tabulated. The point of endocrine interest is that the diabetic aortae differ from non-diabetic aortae in having exaggerated lipid changes and more calcification.—J. C. D.

The symptomatology of diabetes mellitus; an analysis of 1700 cases. Murray-Lyon, R. M., Edinburgh Med. J. **40:** 293. 1933.

This series excluded simple glycosurias, conditions associated with pregnancy and with obvious endocrine disorders aside from the pancreas. Seventeen hundred cases of true diabetes mellitus were reviewed and divided into three groups—obese, arteriosclerotic, and "toxic." The sex incidence of the whole series showed 64.5% females. An hereditary or familial factor was found in 16.3%, there being no significant difference between the three groups. Males tend to develop the disease at an earlier age. Although the cardinal symptoms of diabetes were seen to be the same in all the three classes, significant differences were noted in regard to visual disturbances, gangrene, neuritic pains, sex incidence, and age at onset and type of onset. Two hundred and twenty-four cases of non-diabetic glycosuria showed a male preponderance and earlier incidence. Of these latter patients 32.6% were symptomless as compared with only 2% of the patients who had true diabetes. Of the symptomless glycosurias 31.7% proved to be true diabetes mellitus.—J. C. D.

Metabolism in pregnancy; blood sugar changes during delivery. Rowe, A. W. and Mary McManus, Proc. Soc. Exper. Biol. & Med. **31:** 32. 1933.

The low blood sugar levels characteristic of pregnancy prevail during labor and apparently to within a few minutes of delivery. There is a marked rise in blood sugar on emptying the uterus, the average increase being slightly more than 30%, and in individual cases reaching low hyperglycaemic levels. The time factor as such seemingly plays no part. In the case with blood taken 15 minues before delivery, the level was 85 mg.; 45 minutes later it was 108 mg., an increase of 27%.—Authors' Summary.

The relation of the blood sugar to the symptoms of the insulin reaction; with a discussion of the mechanism of hypoglycemia. Rudy, A., M. J. & Rec. **137:** 463. 1933.

Most of the symptoms of the insulin reaction can be explained by the direct or indirect effect of the drop in the blood sugar on the human body. The symptoms and mechanism of the insulin reaction are closely related to the symptoms and mechanism of the hypoglycemias of any origin. Glucose is the most important remedy for the relief of the insulin reaction. There are two stages in the hypoglycemias of any origin. They are both brought about by the drop in the blood sugar. The first stage is characterized by an activation of the sympathetic nervous system with hypersecretion of epinephrine. The second stage is a result of the effect of the low blood sugar on the central nervous system. Three charts are given to illustrate the mechanism of the blood sugar regulation and the mechanism of the insulin reaction.

—Author's Summary.

Insulin therapy in post-pellagrous trophic ulcers. Sullivan, E. A., New England J. Med. **209:** 241. 1933.

This is a case report in which the patient was rapidly relieved and eventually cured by insulin, in doses of 6 units daily.—J. C. D.

Surgical attempts at increasing sugar tolerance. de Takats, G. and F. P. Cuthbert, Arch. Surg. **26:** 750. 1933.

Four series of experiments have been conducted in the normal dog with the object of increasing sugar tolerance: (1) Ligation of the tail of the pancreas, (2) ligation of the tail of the pancreas with denervation of the adrenals, (3) denervation of the liver, and (4) coeliac ganglionectomy. The rise in tolerance as determined with intravenous injections of dextrose at timed rates comes on gradually following the ligation of the tail of the pancreas. The peak is reached from the third to sixth month after operation and later declines to a level slightly above the normal. The atrophy of the ligated tail produces a superregeneration of the unligated portion, which may even be accentuated by removal of the ligated part. This superregeneration is not maintained, but a gradual adaptation to the functional requirement of the normal dog takes place. Two observations on diabetic children did not indicate that the original diabetogenic factor had been excluded, but it did prove that not only the normal, but the diabetic pancreas is capable of regeneration. As an enlargement of the adrenals was noted in four of six dogs that came to autopsy not earlier than a year after the tail of the pancreas had been tied, adrenal denervation was added to the pancreatic tail ligation. This resulted in a rise of sugar tolerance similar to that observed in the first series, except that there was no decline in the tolerance after six months, a steady high level being maintained until the eighth month, the end of the observation. It was also found that adrenal denervation produced a marked hypersensitivity to insulin, a fact previously observed by several workers. Denervation of the liver did not affect sugar tolerance or alter the shape of epinephrin and insulin curves. Coeliac ganglionectomy produced the most rapid and greatest increase in tolerance. This rise in tolerance has been maintained at the end of one year. An average tolerance of 3.4 grams of dextrose per kilo per hour has been reached, the preoperative level never exceeding 2 grams of dextrose per kilo per hour. Insulin hypoglycemia was markedly increased and epinephrin hyperglycemia curves were flattened. If the experiments on the nervous control of carbohydrate metabolism are to have a clinical application, they would have to be based on the acceptance of a hyper-irritability of the sugar-secreting mechanism in the liver, at least in certain types of diabetes; in other words, on the "overproduction" theory of von Noorden.—Authors' Abst.

Hypoglycemia and hyperinsulinism. Tedstrom, M. K., Ann. Int. Med. **7:** 1013. 1934.

Spontaneous hypoglycemia may be secondary to any disturbance of the blood sugar regulatory mechanism, but it is frequently secondary to hyperfunction of the pancreatic islets following hyperplasia or tumor growth or simple functional changes. It is possible that some relief of menstrual pains, weakness and nervousness, will result from treatment directed toward increasing the blood sugar. All epileptics should have blood sugar studies made, as there seems to be a small number whose convulsions are secondary to hypoglycemia. Medical treatment consists chiefly in dietary regime to prevent lowering of the blood sugar level. If medical treatment is unsuccessful, surgery should be resorted to. If no tumor is found, resection of more than half of the pancreas is justified. Apparently too small a portion of the pancreas has been removed in previous cases.—Author's Summary.

Studies on the physiology of the parathyroid glands; renal complications of hyperparathyroidism. Albright, F., P. C. Baird, O. Cope and Esther Bloomberg, Am. J. M. Sc. **187:** 49. 1934.

The renal lesions in hyperparathyroidism were divided into three types, viz.: Type I—stone formation in renal pelves, leading to pyelonephritis; Type II—precipitation of calcium in renal tubules, leading to renal sclerosis; and Type III—precipitation of calcium salts in kidney parenchyma as one of several organs, in parathyroid poisoning. A review of 83 cases of hyperparathyroidism revealed 23 patients with Type I lesions, 19 patients with Type II lesions, and

one patient with Type III lesions. Cases were cited from the authors' own cases where kidney lesions existed without bone lesions. Metabolic studies were made on two patients with Type II lesions and revealed certain differences from the findings in similar studies on patients with hyperparathyroidism but with renal involvement, viz.: (a) Hypophosphatemia was not present (b) the degree of hypercalcinuria was decreased; (c) the fecal calcium excretion was increased rather than decreased; (d) the partition of phosphorus in the urine as compared with the feces was less elevated.—Authors' Abst.

Parathyroid tumors associated with hyperthyroidism; eleven cases treated by operation. Churchill, E. D. and O. Cope, Surg., Gynec. & Obst. **58**: 255. 1934.

Hyperparathyroidism is a distinct disease entity associated with a definite train of symptoms and a characteristic disturbance of calcium and phosphorous metabolism. It is constantly associated with a demonstrable adenoma usually of gross size of one or more parathyroid bodies. Following the total or subtotal resection of the tumor the calcium and phosphorus metabolism returns to normal, usually after a more or less prolonged period of tetany. The beneficial effects said to follow the removal of one or more normal parathyroids in certain cases of arthritis or in Paget's disease are, to say the least, viewed with skepticism. The plan of operation in a proved case of hyperparathyroidism is outlined. The method of dealing with parathyroid tumors contained in the mediastinum is described and two such cases are reported. The removal of normal parathyroid bodies or interference with their blood supply when operating with a definite diagnosis of hyperparathyroidism is absolutely contraindicated. Subtotal resection of a parathyroid tumor is advisable when normal glands have been removed or damaged at a previous operation. Subtotal resection may also prove to be the operation of election in a very sick patient to lessen the dangers of severe tetany. It has been done in one such case. The fate of the residual tissue being unknown at the present time, complete resection is the operation of choice. Case histories of 11 patients with hyperparathyroidism in which an adenoma was removed at operation are appended.—Authors' Summary.

Contribution to the knowledge of parathyroid activity (Beitrage zur Kenntnis der Epithelkörper-Wirkung). Herzfeld, E. and A. Frieder, Klin. Wchnschr. **11**: 1262. 1932.

The parathyroid glands were removed immediately after slaughtering and dried quickly in vacuo. Intramuscular injection of a glycerin emulsion of the dried glands in doses of 30 to 60 mg. into 8 normal dogs raised the blood calcium from normal levels of 5.6-9.9 to 7.4-11.8 with an intervening negative phase. The percentage increases in the calcium level varied from 20 to 57%. Oral administration of the dried glands (20 to 50 mg.) to 18 normal dogs raised the blood calcium from normal levels of 8.1-10.0 to 9.2-12.3 with an intervening negative phase. Rectal administration was similarly effective. Subcutaneous administration of the glycerin emulsion to 6 parathyroidectomized cats kept them alive and free from tetany during an observation period of 14 days.—C. A. Dragstedt.

Parathyroidectomy in generalized osteitis fibrosa cystica; report of a case in a child 2½ years of age. Landon, J. F., J. Pediat. **1**: 544. 1932.

A report is made of a case of parathyroidectomy in a child. The patient was a male, 2½ years of age, with the following salient points in the history: He had a swelling of the left jaw at the age of 6 months, and of the left side of the head at 11 months. Both were incised and drained. For the past 6 months the child disliked being handled and limped slightly. On physical examination he presented the following: Over the condyle of the left humerus there was a firm, somewhat elastic immobile swelling. The left leg was shorter than the right. There was tenderness on deep pressure on the legs. X-ray examination of the skeletal system showed what appeared to be cystic degeneration in skull, left and right humeri, right radius, heads of both humeri, pelvis, both femora, both tibiae and right astragulus. Diagnosis was made of osteitis fibrosa cystica with generalized glandular enlargement. The blood calcium ranged between 10.5 and 19.4 mg. per 100 cc., with increasing values for the next three months. Phosphorus was 2 to 3 to 5.5 mg. per 100 cc. at the same time that Viosterol was given from 5 to 10 minims t.i.d. Three months

after admission a small mass was palpated near the left thyroid. On operation small masses were removed and found to be parathyroid tissue and lymph glands. There was clinical and x-ray improvement but no change in calcium or phosphorus values following the operation. The presence of relatively high calcium and low phosphorus content not affected by operation is in accord with two cases quoted by Hunter in which normal parathyroid tissue was removed without changes in either calcium or phosphorus.—M. B. G.

The histological changes in the bone responsible for the action of parathyroid hormone on the calcium metabolism of the rat. Pugsley, T. I. and H. Selye, J. Physiol. **79:** 113. 1933.

An investigation of the validity of the theory that immunity of experimental animals to parathormone results from proliferation of osteoblasts or disappearance of osteoclasts. Rats on a standard diet were given 20 units daily of parathormone. Serum calcium and urine calcium excretion determinations were made daily; also one rat was sacrificed daily for bone examination. The serum calcium and urine calcium values were restored to normal when the osteoclasts disappeared from the bone marrow.—C. I. R.

Observations on human subject 5 years after splenectomy (Observaciones fisiológicas alejadas en un joven esplenectomizado). Combes, T. J. C., Rev. Soc. argent. de biol. **9:** 186. 1933.

The red cell count was 4.4 million and did not vary with exercise. The hemoglobin and globulin values were normal. The white cell count was 13,000. The neutrophiles were 54%, acidophiles 9%, basophiles 1%, lymphocytes 30%, and monocytes 7%. Duration of voluntary apnea was not increased with successive efforts as in normal subjects. The basal metabolism was normal. Puberty occurred after the operation (at the time the subject, a boy, was 12 years old) without abnormality. It is concluded that the function of the spleen as a red cell reservoir is not taken up by another organ and that the spleen plays no significant part in normal puberty.—J. T. L.

Preparation, properties and occurrence of an anti-thyroid protective substance in blood and tissues (Darstellung, Eigenschaften und Vorkommen einer antithyreoiden Schutzsubstanz aus Blut und Geweben). Anselmino, K. J. and F. Hoffmann, Klin. Wchnschr. **12:** 99. 1933.

The authors report on studies of CO_2 production, liver glycogen and acetone bodies in the blood (Engfeldt method) in young albino rats (4 control and 4 experimental in each series). Five doses of 0.028 mg. thyroxine were injected in 2-3 days after the rats had received, in their food, an ether-acetone extract of 20 cc. of serum in 0.8 cc. of olive oil. Control rats received only the olive oil. CO_2 production increased 34% in the controls and remained unchanged in the experimental group. The relative content of anti-thyroid protective substance in 100 cc. of serum was—fetal blood 8, normal adult blood 5, blood in pregnancy 3, blood in Basedow's disease less than 4, animal blood less than 3; in 100 gm. tissue—marrow 100 plus, ovary 50, liver 25, thymus 25, etc. The extract prevented the usual diminished liver glycogen content and increase of acetone bodies in blood after thyroxine injection. In normal animals the liver glycogen increased and the acetonemia diminished when the extract was fed. The administration of thyreotropic hormone of the anterior pituitary (Thyreotropin Schering-Kahlbaum) diminished the liver glycogen in the controls while in animals fed with the anti-thyroid extract the liver glycogen content was higher than in the normal rats. To date only a small group of patients with Basedow's disease have received the extract, and with varying results.—R. A. Phillips.

The effect of giving single doses of thyroid gland to chickens and the determination of iodine in tissues (Über das Schicksal des Schilddrüsenhormons im Organismus hyperthyreoidisierter Tiere; Hyperthyreoidisation von Hühnern mit einmaligem Schilddrüsendosen und Bestimmung von Jod in Geweben). Asimov, G., E. Estrin and S. Miletzkaja, Ztschr. f. d. ges. exper. Med. **76:** 409. 1931.

The authors observed the amount of iodine present in the various tissues of hens and cocks (24 in all) after feeding dried thyroid gland by mouth. There was an increase in all tissues, the greatest amount being present in

thyroid and yolk and the least in brain and sex organs (Kendall-Richardson method). The presence of thyroxine in the tissues of these fowls was demonstrated by observing the implantation of organ tissue into Axolotls. In the fowl more thyroid hormone is stored in the tissues in the winter than in the summer.—R. A. Phillips.

The fate of the thyroid hormone in animals fed with thyroid substance; the method of excretion of the thyroid hormone after feeding dried thyroid to dogs (Über das Schicksal des Schilddrüsenhormons im Organismus hyperthyreoidisierter Tiere; der Charakter der Ausscheidung des Schilddrüsenhormons nach peroraler Einführung getrockneter Schilddrüse beim Hunde). Asimov, G. and E. Estrin, Ztschr. f. d. ges. exper. Med. **76:** 380. 1931.

Observations were made on 2 dogs, both with gall-bladder fistula and one with ureteral fistula, of the iodine content of the bile and urine after feeding dried thyroid gland. The methods used by Kendall were employed. They found, however, that the concentration of iodine was higher in the urine in both cases but that the increase in iodine content starting 30 minutes after feeding, reaching a maximum in 12-17 hours and then slowly receding is roughly parallel in bile and urine. Of interest is the observation that this post-prandial bile effected metamorphosis, to some degree, in about one-third of the number of injected Axolotl's (46 injections), while in no instance (34 injections) did the urine effect metamorphosis of the Axolotl. The authors find that the iodine salt concentration occurring in the kidney does not occur when hydronephrosis is present.—R. A. Phillips.

The method of excretion of the thyroid gland hormone after the ingestion of thyroxine (Über das Schicksal des Schilddrüsenhormons im Organismus hyperthyreoidisierter Tiere; der Charakter der Ausscheidung des Schilddrüsenhormons nach Einflührung von Thyroxine per os). Asimov, G. and E. Estrin, Ztschr. f. d. ges. exper. Med. **76:** 399. 1931.

In addition to verification of previous observations of the authors the following conclusions are drawn (studies on 2 dogs). The experiment in general was the same as previously described except that thyroxine, per os, was studied. (1) With normal kidneys the secretion of iodine in the bile and urine is about equal but with kidney damage the majority is secreted by the bile. (2) The inability of the sclerosed kidney to concentrate iodine salts is demonstrated. (3) The iodine content of the blood is not increased appreciably. (4) Thyroxine passes through the liver into the bile in practically an unchanged fashion, while in the urine the iodine present is in a simple compound form (Axolotl metamorphosis as criteria).—R. A. Phillips.

The pathologic anatomy of the liver in exophthalmic goiter. Beaver, D. C. and and J. deJ. Pemberton, Ann. Int. Med. **7:** 687. 1933.

Analysis was made of the pathologic anatomy of the liver and the correlated clinical findings in 107 cases of exophthalmic goiter. Three types of hepatic lesions predominate in exophthalmic goiter: (1) Acute degenerative lesions (fatty metamorphosis, focal and central necrosis, and changes secondary to stasis of blood); (2) simple atrophy, and (3) subacute toxic atrophy and toxic cirrhosis. The frequency of these lesions was as follows: (1) Acute lesions, 91.5%, of which fatty metamorphosis composed 87.8%, central necrosis 50.4%, and focal necrosis 5.6%; (2) atrophy 63.55%, in which cases the average weight of the liver was 1,316 gm. and (3) subacute toxic atrophy and cirrhosis 59.81%, of which lesions of grade 1 composed 44.86%, lesions of grade 2, 12.15%, lesions of grade 3, 1.87%, and lesions of grade 4, 0.93%. Jaundice was present in 23 cases (21.5%). The hepatic lesions are usually adequate to account for the presence of icterus, and in addition, including cases without jaundice, they are sufficient probably to cause disturbances of hepatic function detectable by clinical tests of hepatic efficiency in approximately 40% of the cases. The common factor in the evolution of these lesions appears to be severity of the syndrome of exophthalmic goiter. The acute lesions are not usually influenced in their occurrence or severity by the age of the patient, the sex, or the percentage loss of body weight. Except for the loss of body weight, the acute lesions usually occur directly in proportion to severity of the disease. They appear most prominently in the more severe cases of shorter than average duration. Atrophy is more pronounced among females than males, and appears to be more marked among the aged than the young. It is propor-

tional to severity of the disease, with the exception that it seems not to be correlated with basal metabolic rate. The duration of the disease does not appear to be a factor. The smaller livers were observed in the smaller subjects, and the larger livers in the larger subjects. The relationship of the weight of the liver to loss of body weight, however, will constitute an independent study. The changes of subacute toxic atrophy and cirrhosis appear more frequently among females than males but the difference in incidence, according to sex, is not greater than in the entire study. These lesions appear among older patients, among whom the disease is of longer duration and more severe than average. The authors concluded, as Boothby did in speaking of jaundice in exophthalmic goiter, that in most instances the lesions in the liver appear to be an integral part of the syndrome of exophthalmic goiter, and that they are due directly to thyroid intoxication, since, as the authors have found, they are usually intimately related in their severity, to the intensity and the duration of the disease. It is probable that the hepatic changes are not only related to the hyperthyroid state, but also to the toxic factor of exophthalmic goiter, which Plummer believes exists, for in experimentally produced hyperthyroidism, induced in animals by feeding thyroid substance, lesions comparable to those the authors have described have not been produced. Atrophy, acute degeneration, and cirrhosis are probably interrelated conditions, each with a sequential pathogenetic relationship to the other, and each intimately concerned with the hyperthyroid state and the toxic factors as elaborated in the syndrome of exophthalmic goiter.—Authors' Abst.

Low basal metabolic rates. Carey, J. B. and Helene Paine Brumfield, Minnesota Med. **16:** 396. 1933.

From a study of 489 cases showing a basal metabolic rate of —10 or less in 2,500 consecutive cases (patients having myxedema were not included), Carey and Brumfield conclude that: (1) Patients presenting certain symptoms of fatigue, general aches and pains of the body and apprehensive anxiety states should have basal metabolic rate determinations. (2) It may be helpful as a guide to therapy in certain postinfectious states and at the menopause. (3) Such determinations should be made as a part of the study of male or female sterility when no organic or functional cause is found. (4) Such study should be made in all women suffering from menstrual abnormalities not explained on an organic basis. (5) Cases of habitual abnormal pregnancy should likewise be so studied. When a low basal metabolic rate is found in any of these conditions, thyroid substance should be administered to an extent and for as long as seems sufficient to raise the rate to normal and to maintain it. It should be discontinued only if not tolerated, or after a sufficient length of time has elapsed so that it can be certainly declared ineffective. The authors' percentage of improvement in the treated patients with adequate follow-up (62.8%) supports this belief, which is further strengthened by the results in the treatment of sterility and threatened abortion. Pregnancy occurred in seven of 29 sterile women. Eleven patients had no adequate follow-up. Successful pregnancies resulted in four of five patients with threatened abortion or in whom abortions had occurred in previous pregnancies.—Authors' Abst.

Thyroid disorders in childhood. Cattell, R. B., New England J. Med. **209:** 867. 1933.

The author reviews the subject and states that disorders of the thyroid in children are not unusual. Advice will be frequently sought of the physician regarding the presence or absence of colloid goiter and the treatment for it. Small quantities of iodine given for a short period semiannually are sometimes of benefit in colloid goiter and do no harm. Hyperthyroidism will be encountered with the same clinical characteristics as in adults and subtotal thyroidectomy should be done, the results of which are very satisfactory. The other disorders are more rarely encountered and although sporadic must be recognized and properly treated if these children are to develop normally.

—J. C. D.

The mechanism of the action of thyroxine in tissue metabolism (Über den Wirkungsmechanismus des Thyroxins beim Gewebestoffwechsel). Ebina, T., Tohoku J. Exper. Med. **19:** 139. 1932.

Using the author's modification of the Warburg technique the influence of thyroxine in vivo and in vitro on the respiration and anerobic glycolysis of kidney and liver tissue of the rat was studied. In vivo there is a definite stimulative effect except in the case of the liver anerobic glycolysis. In vitro

there is a stimulative action in all instances. The work corroborates Haffner's hypothesis and also indicates that thyroxine has a definite peripheral action.
—R. A. Phillips.

The basal metabolic rate and the suspension stability of blood (Relación entre el metabolismo basal y la eritrosedimentación [300 determinaciones]). Goldemberg, L., Rev. Soc. argent. de biol. **9:** 393. 1933.

Simultaneous determinations of the basal metabolic rate and the suspension stability of blood were made in 195 cases showing increased, decreased or normal thyroid function. In 85 cases, the basal metabolic rate and the suspension stability were normal; in 34, the basal metabolic rate and the suspension stability were increased; in 38, the basal metabolic rate was normal and the suspension stability increased, due to infections, pregnancy, etc.; in 24, the basal metabolic rate was increased, due to hyperthyroidism, but the suspension stability was normal. These latter responded more easily to treatment than those with increased suspension stability. In 14 cases with lowered basal metabolic rate variable results were obtained with the suspension stability determinations and no conclusions can be deduced.—J. T. L.

Thyroidectomy in the treatment of advanced congestive heart failure and angina pectoris. Levine, S. A., E. C. Cutler and E. C. Eppinger, New England J. Med. **209:** 667. 1933.

Detailed case histories and their analyses are given. Part or complete removal of the normal thyroid gland was performed in 12 patients suffering from the most severe forms of heart disease. There were four with angina pectoris, four with valvular heart disease and auricular fibrillation, and four with non-valvular congestive heart failure. They were all hopeless cardiac cripples and, for the most part, bedridden. Improvement in six was marked. In three, it was slight to moderate. In one, there was no improvement. In one, sufficient time has not elapsed to judge. There was one operative mortality in a patient who was moribund at the time of operation. The most promising group at present seems to be those patients suffering from angina pectoris.
—J. C. D.

The diagnositic use of iodine in thyrotoxicosis. Means, J. H. Ann. Int. Med. **7:** 439. 1933.

Iodine is not useful solely in the treatment of toxic goiter, but also, by virtue of its utterly characteristic action in that disease, it is helpful in diagnosis as well. Given a goiter, the doctor must answer three questions: Is it producing thyrotoxicosis? Is it making pressure? Is it malignant or likely to become so? The first is usually easily answered, but not always. When there is doubt, establishment of the basal metabolic level by repeated determinations on successive days and then noting the effect of giving iodine, is informative. If thyrotoxicosis is present, the metabolism will show a significant fall, even though the initial level was not above standard. Furthermore, on omission of iodine, it will return to its original level. These remissions and relapses, coinciding with iodine and no-iodine periods, are diagnostic of the thyrotoxicosis. Also in postoperative cases, so long as such iodine fluctuations occur, thyrotoxicosis must be presumed to persist.—Author's Abst.

The mode of action of thyroxine (Untersuchungen über den Wirkungsmechanismus des Thyroxins). Stockheim, W., Arch. f. d. ges. Physiol. **228:** 469. 1931.

Studies on 8 dogs (old and young, male and female) are reported. "Thyroxin-Schering" was fed daily to 6 animals for from 4-14 days, dosages varying from 0.115-1.25 mg. daily. The animals were on a regular diet. In the liver an increase of fatty infiltration and water content was observed coincidental with a diminution of glycogen. In the skeletal and heart muscle no definite change of glycogen content was observed, but there was an increase of water content in the heart muscle. Two animals were fasted for 11 days and 1.25 mg. thyroxine fed daily the last 3 days; no definite variations in glycogen content in liver, heart muscle or skeletal muscle was observed. In both experiments was observed—(1) a normal total nitrogen and a diminished resting N-content of the liver, (2) a definite increase of the relative kidney weights, (3) a definite increase of blood sugar, (4) a definite diuretic action with an increase of the total N-content of the urine. The individual variations and their import are discussed.—R. A. Phillips.

Induction of typical pseudopregnancy in the albino rat by means of experimental hyperthyroidism. Weichert, C. K. and R. W. Boyd, Anat. Rec. **58**: 55. 1933.

Female rats fed doses of 0.25 gm. or 0.5 gm. of desiccated thyroid daily have 0, 1, 2 or 3 regular oestrous cycles after the beginning of thyroid feeding followed by a prolonged dioestrous period 10 to 22 days in duration. (Average 13.24 days.) A series of such dioestrous periods occurs as long as thyroid feeding is continued, these prolonged intervals being separated from each other by one or two normal oestrous periods. If thyroid feeding is discontinued during such a prolonged dioestrous period, normal and regular oestrous cycles again follow. That the prolonged dioestrous intervals are true pseudopregnant periods is indicated by their average length and by the appearance of the ovaries and vaginal mucosa. The large corpora lutea present are functional as is indicated by the experimental production of placentomata during the pseudopregnant period. Two explanations are offered: (a) The administration of desiccated thyroid gland stimulates the anterior lobe of the pituitary body to elaborate its hormone or hormones which bring about the formation and persistence of large functional corpora lutea. (b) The heightened metabolism resulting from thyroid feeding may lower the oestrin concentration to such a degree that the function of the corpora lutea may be expressed.—Authors' Abst.

Induction of typical pseudopregnancy in the albino rat by means of experimental hyperthyroidism. Weichert, C. K. and R. W. Boyd, Anat. Rec. **58**: 55. 1933.

Twenty-three normal female rats were fed 0.25 gm. or 0.5 gm. of desiccated thyroid daily for periods ranging from 31 to 52 days. Daily records of vaginal smears were kept. After having 0, 1, 2, or 3 regular oestrous cycles after the beginning of thyroid feeding, prolonged dioestrous periods occurred 10 to 22 days in duration (average 13.42 days). Similar dioestrous periods recurred as long as thyroid feeding was continued, the periods being separated from each other by one or two normal oestrous periods. If thyroid feeding were discontinued during one of the prolonged dioestrous periods, normal and regular oestrous cycles again followed. The length of the prolonged dioestrous intervals and the appearance of the ovaries and vaginal mucosa suggested that probably typical pseudopregnant periods were occurring This suggestion was confirmed by the experimental production of placentomata in nine additional animals during a pseudopregnant period brought on by thyroid feeding. Two explanations are offered: (1) Under the hyperthyroid condition resulting from thyroid feeding the anterior lobe of the pituitary is stimulated to elaborate its hormones which in turn exert a luteinizing effect on the ovary producing large and functional corpora lutea. (2) The heightened rate of metabolism under hyperthyroid conditions may cause a lowering of the oestrin concentration to such an extent that the corpora lutea may express their function.
—Authors' Abst.

Gastric acidity in thyroid dysfunction. Wilkinson, S. A., J. A. M. A. **101**: 2097. 1933. Abst., A. M. A.

The relationship between hyperthyroidism and gastric acidity was studied to determine to what extent the acid returned to its normal level after relief of the toxicity and to see what effect a postoperative lowering of the basal metabolic rate below the normal level would have on gastric acid. His study comprises the results of gastric analyses in 100 cases of hyperthyroidism, taken before operation. He found that of the 100 cases of hyperthyroidism, 36% showed achlorhydria, and the average acid of all cases was reduced to slightly more than half the normal. The observation is made that the incidence of achlorhydria in hyperthyroidism rises in proportion to the duration of the toxicity rather than the degree of the toxicity. After thyroidectomy, only 10.5% show achlorhydria. The average free acid is raised to about the normal value for the entire series. The author believes that the depression of gastric acidity is a phenomenon of extreme sympathetic overstimulation. Hypothyroidism, in his series at least, produced a definite tendency to hyperacidity.

Annual Index

AUTHORS

Aaron, M.: Variation in susceptibility of the thyroid in mammals of different species to the thyroid-stimulating substance of the anterior lobe of the hypophysis and of the ovary to gonadotropic hormone 643

Abbott, A. C.: Simple goiter; its racial incidence and its relationship to nutrition 658

— Simple goiter; the incidence of thyroid enlargement in Winnipeg school children 657

— Simple goiter; the relationship between chronic foci of infection and simple thyroid enlargement in children....658

— (Goodwin and Meltzer): The effect of tracheal compression on the thyroid gland..658

Abe, M.: Placental enzymes in various stages of pregnancy...284

Abelin, I. (Wiedner): Thyroid and ovary 548

Aberle, S. B. D.: The interrelation of a gonotropic hormone and vitamin A 743

Adamcsik, A. (von Beznak): The effect of parathyroid hormone on the calcium content of the milk of women 159

Aeschlimann, H.: The diagnostic value of phagocytosis in thyroid disease 305

Albright, F. (Baird, Cope and Bloomberg): Studies on the physiology of the parathyroid glands; renal complications of hyperparathyroidism 760

— (Bauer, Claflin and Cockrill): Studies in parathyroid physiology; effect of phosphate ingestion in clinical hyperparathyroidism 302

— cf. Baird 275, 550

Alden, C. R.: The use of pituitary extract in obstetrics 750

Alexander, S. L.: cf. Gilchrist...650

Allan, F. N. (Scherer): Insulin resistance due to allergy.....157

Allen, E.: Hormone control of changes in the endometrium during the menstrual cycle....284

— Sex and internal secretions...423

— cf. Overholser 549

Allen, F. M.: Insulin in treatment of tuberculosis 648

Allen, W. M.: cf. Reynolds.....289

Alper, J. M.: cf. Thompson..228, 665

Alperstein, B. B.: cf. Goldzieher.505

Andersen, W. T.: On the occurrence of spontaneous glycosuria and alimentary hyperglycaemia in exophthalmic goiter 447

Anderson, H. (Kennedy): The effect of gonadectomy on the adrenal, thyroid and pituitary glands 744

Anderson, Dorothy H. (Kennedy): Studies on physiology of reproduction; changes in adrenal gland of female rat associated with oestrous cycle 143

Anderson, E. M. (Collip): Thyreotropic hormone of anterior pituitary 291

Anderson, Evelyn M.: The production of hyperplasia of the thyroid with hyperthyroidism in the albino rat.....658

— cf. Collip 639

Anderson, W. E.: cf. Reed.....150

Andrus, E. C.: Clinical and experimental observations upon the heart in hyperthyroidism..447

Anido, B.: cf. Mussio Fournier..533

Annau, E. (Huszak, Svirbely and Szent-Györgyi): The function of the adrenal medulla 739

Anselmino, K. J. (Hoffman): Preparation, properties and occurrence of an anti-thyroid protective substance in blood and tissues 762

Arguelles, G.: cf. Marañon.....497

Arloing, F. (Morel, Josserand and Badinand): Further studies on the tumor-inhibiting properties of adrenal extracts tested on experimental epithelioma in white mice 633

von Arnay, A. (Lengyel): Lactic acid formation during muscular work after removal of suprarenal glands 275

Artundo, A. (Solari): Effect of anterior pituitary extract on basal metabolism 750

— cf. Houssay 660, 752

v. Arvay, A.: cf. Verzár 297

Aschner, B. (Jaso-Roldan): The clinical significance of pituitrin-hyperglycemia 755

Asher, L. (Tschumi): Studies on physiology of glands. Further experiments on relationship between spleen and thyroid and iron metabolism 306

Asimov, G. (Estrin): The fate of the thyroid hormone in animals fed with thyroid substance; the method of excretion of the thyroid hormone after feeding dried thyroid to dogs.....763

— — The method of excretion of the thyroid gland hormone after the ingestion of thyroxine 763

— (Estrin and Miletzkaja): The effect of giving single doses of thyroid gland to chickens and the determination of iodine in tissue 762

Athias, M. (Guimarais): Intracranial ovarian grafts in normal male guinea pigs and ones which had been previously castrated..547

Atkinson, R. F. B.: The onset of acromegaly before 15 years of age 643

Atwell, W. J.: cf. Emery.....740

Aubertin, E. (Trinquier): The hypoglycemia effect of insulin injected into the portal system of dogs 648

— — The use of the area of hypoglycemia in the study of the hypoglycemia action of insulin in dogs 648

Ayer, J. B. (Means and Lerman): Simulation of progressive muscular atrophy by exophthalmic goiter 701

Azérad, E.: cf. Labbé.....312

Azevedo, G. V.: The use of insulin in the treatment of menorrhagias of ovarian etiology and in particular in hemorrhagic metropathy 442

Babarczy, Marie V.: Relation between the cholesterol content of the blood and adrenaline sensitivity 143

Bacq, Z. M.: A note on the viale reaction of demonstrating adrenine in body fluids 633

— Secretion of sweat in horses after cutaneous injections of adrenine serum.....633

— (Brouha): Certain new facts about the humoral effects of exciting the sympathetic....633

Badinand, A.: cf. Arloing.....633

Bailly, O. (Netter): Researches on carotene; carotene of the adrenal gland 739

Baird, P. C. (Albright): Treatment of Addison's disease with cortin (Hartman); report of four cases 275

— (Cloney and Albright): Effect of cortical hormone in preventing extreme drop in colonic temperature displayed by hypophysectomized rats upon exposure to cold with preliminary observations upon the effect of hypophyseal and other hormones 550

— cf. Albright 760

Bakacs, G.: Simultaneous use of parathyroid hormone and calcium in abnormal uterine bleeding 653

Ball, R. G.: cf. Camp.....143

Barbour, O.: Treatment of coughs with suprarenal; whooping cough 739

Barnard, W. G.: A functioning tumor of the islands of Langerhans 157

Barnes, A. R.: cf. Kepler.....311

Barnes, B. O. (Regan and Nelson): Improvement in experimental diabetes following administration of amniotin.....649

— cf. Bueno 152

— cf. Jones 310

— cf. Mathieu 313

— cf. Regan 159

Barrelet, J.: Endocrine glands in cirrhosis of liver 280

Bartschi, W.: cf. Guyenot.....640

Bates, R. W.: cf. Kurzrok..... 18

— cf. Riddle 155, 156

Battistini, S. (Rigoletti): Modifications of glycemia, blood pressure and pulse after intravenous injection of insulin in subjects with normal carbohydrate exchange 756

Battro, A.: cf. Castex.....307

Bauer, J. (Buttu): Effects of adrenal cortical extracts upon the blood in men 633

Bauer, W.: cf. Albright 302

Beaver, D. C. (Pemberton): The pathologic anatomy of the liver in exophthalmic goiter 763

Becher, H.: Effect of incretions on the motility of mammalian sperms 546

di Benedetto, E.: Anterior pituitary lobe and action of insulin.433

— Extract of anterior lobe of the hypophysis and resistance to insulin 643

— cf. Houssay .....
...295, 437, 438, 552, 553, 645

— cf. Rossignoli 314

Benedict, F. G.: cf. Riddle.....283

Bennholdt-Thomson, C.: On mongolianism and other congenital degenerative conditions in their relation to advanced age of the mothers 636
Berblinger, W.: Pathologie und pathologische. Morphologie der Hypophyse des Menschen.....274
Berlin, D. D.: cf. Blumgart.....448
Bernhardt, H. (Simpson): Relation of suprarenal cortex to myasthenia gravis pseudoparalytica 543
Bernstein, C.: cf. Duff.....740
Best, C. H. (Ferguson and Hershey): Choline and liver fat in diabetic dogs 756
— (McHenry): The Friedman modification of the Aschheim-Zondek test for diagnosis of pregnancy 547
von Beznak, A.: cf. Adamcsik...159
Bialet-Laprida, Z.: Effect of folliculin on adult ovary 744
— Effect of folliculin on development of ovary 744
Biasotti, A.: cf. Houssay.....294, 295, 310, 437, 438, 553, 645, 660
Bing, J.: Sporadic goiter on genotypical basis and relation to other thyroid disorders 306
Bischoff, F. (Long): Effect of adrenaline upon free muscle sugar and total carbohydrate..635
— (Maxwell): Hormones in cancer; the effect of glandular extirpation upon the growth of transplantable tumors ..742
— cf. Long 635
— cf. Maxwell 743
Bishop, P. M. F. (Close): A case of basophil adenoma of the anterior lobe of the pituitary: "Cushing's Syndrome" 152
Blades, E. J.: cf. Herrick.....310
Bloomberg, Esther: cf. Albright.760
Blotevogel, W.: Effect of Roentgen rays on the ovaries and ganglion cervicle uteri 547
Blotner, H.: Insulin and sugar tolerance in thin people.....756
— The treatment of diabetes....442
Blumenfeld, C. M.: Weight changes in suprarenal gland of albino rats on Vitamin E deficient and fat deficient diets....367
Blumgart, H. L. (Davis): Hypothyroidism induced by complete removal of the normal thyroid gland in the treatment of chronic heart disease 693
— (Levine and Berlin): Congestive heart failure and angina pectoris: the therapeutic effect of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity 306
Blumgart, H. L. (Riseman, Davis and Berlin): Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris; early results in various types of cardiovascular disease and coincident pathologic states without clinical or pathologic evidence of thyroid toxicity 448
Böhm, F.: Influence of anterior lobe of hypophysis on blood sugar content 291
Bohstedt, G.: cf. Kozelka.....655
Borras, P. E.: Friedman's reaction for the diagnosis of pregnancy 285
Borst, M. (Döderlein and Gostimirovic): Sex physiology. VI. Ovulation induced by the luteinizing hormone, prolan B.....285
Bowie, N. A.: cf. Derick.....649
Boyd, R. W.: cf. Weichert.....766
Brabant, H.: cf. Watrin.....291
Bradley, H. T.: cf. Noble.....743
Braier, B.: Nitrogen metabolism in hypophysectomized dog.....292
— Pituitary and nitrogen metabolism in toads 643
Braun, M. E.: Blood pressure in hypophysectomized dogs 292
Brewer, L. A., III: Occurrence of parathyroid tissue within the thymus: Report of four cases.397
Brill, J.: The ovaries and testes of foetal horses as a source for hormones 638
Brindeau, A. (Hinglais and Hinglais): Contribution to the quantitative study of the hormone from the anterior lobe pituitary by use of the adult rabbit; application of biologic measures to the gonadotropic hormone 292
Brosius, W. L.: cf. Engelbach...387
Broster, L. R. (Hill): Adrenogenital syndrome associated with cortical hyperplasia: results of unilateral adrenalectomy 275
Brouha, A.: The inhibitory action of folliculin on deciduomata in rabbits 638
Brouha, L. (Desclin): Note on experimental cryptorchidism in guinea pigs 638
— cf. Bacq 633
Browne, J. S. L.: cf. Butenandt..548
— cf. Collip 71
Brownell, K. A.: cf. Hartman....145
Brull, L.: Transmission by the blood stream of the polyuria and hypochloruria following hypophysectomy 644
Brumfield, Helene Paine: cf. Carey 764

Bryan, W. R. (Minot and Chastain): The occurrence of guanidine as a contributory factor in parathyroid tetany in dogs....159
Buchheim, W.: Effect of fuel oil on the secondary sex characters 285
Bueno, J. G. (Barnes): The effect of Loeb's anterior pituitary extract upon the basal metabolism of dogs 152
Bühler, F.: Influence of sex hormones on creatine metabolism.427
Burn, J. H.: Estimation of antidiuretic potency of pituitary (posterior lobe) extract 292
Burns, R. K. (Buyse): The induction of precocious maturity in the reproductive tract of recently metamorphosed female salamanders by an extract of the mammalian hypophysis ...750
Burns, R. K., Jr.: Follicular atresia in the ovaries of hypophysectomized salamanders in relation to yolk formation.....293
Butenandt, A. (Browne): The female sexual hormone; comparative investigation of theelol, emmenin and follicular hormone hydrate 548
Buttu, G.: cf. Bauer 633
Buyse, A.: cf. Burns.....750

Cadiz, R. (Lipschütz): Concerning a case of masculine pseudo-hermaphroditism 745
Camp, J. D. (Ball and Greene): Calcification of the suprarenal glands in Addison's disease....143
Campbell, A. D.: Further studies on the anterior pituitary-like hormone with special reference to irregular uterine bleeding...551
Campos, C. A. (Curutchet and Lanari): Rôle of the liver in the hyperglycemic activity of the anterior pituitary lobe in toads.433
Canciovici, D.: cf. Nitzescu.....652
Cannon, B.: cf. Rosenblueth.....146
Cantor, M. M. (Scott): Treatment of Addison's disease with extract of adrenal gland 341
Canzanelli, A. (Rapport): The comparative effects upon metabolism of intravenously injected tyrosine, diiodotyrosine, diiodothyronine and thyroxine.....307
Caravati, C. M.: Insulin neuritis; a case report 443
Carey, J. B. (Brumfield): Low basal metabolic rates.....764
Carlson, A. J.: cf. Da Costa.....308
Carr, Katherine: cf. Sherwood...254
Cartolari, C.: Antagonism between thymus and suprarenal medulla 305
Casas, J. (Hinsberg): Insulin sensitiveness and carotid sinus...300
Casida, L. E.: Production of ovulation by gonadotrophic extracts 714
— (Hellbaum): Ovarian stimulation by adrenal extracts.....249
Castex, M. R. (Schteingart and Battro): The heart in hyperthyroidism 307
del Castillo, E. B.: Inhibition of ovulation in rabbit by folliculin.427
Castiglioni, C. A.: cf. Mussio Fournier 533, 656
Catchpole, H. R.: cf. Cole.....548
Cattaneo, L.: Passage of hormones from mother to foetus..638
Cattell, R. B.: Thyroid disorders in children 764
Cernautzeanu-Ornstein, E.: cf. Parhon 657
Chaikoff, I. L. (Lyons): Lactation in diabetes 757
Chambers, W. H.: cf. Dann.....308
Charvat, J.: The non-surgical treatment of Graves' disease...449
Chastain, L. L.: cf. Bryan.....159
Chaykovisky, V. K.: cf. Mandelshtram 639
Chistoni, A.: Chemical and biological investigation of the effective principle of lymph-node extract 281
Choay, A. (Faure): The oestrous-stimulating power of powder from follicular liquid 22 years after drying 639
— (Wurmser): Conservation of oxytocic properties of powdered posterior lobe of hypophysis 293
Chrometzka, F.: Antitrypsin; the hormonal and pharmacological relationship between the albumin-globulin ratio and the antitryptic titer of human serum...147
Churchill, E. D. (Cope): Parathyroid tumors associated with hyperparathyroidism; eleven cases treated by operation.....761
Claflin, D.: cf. Albright.....302
Clark, B. B.: cf. Paul.....158
Clark, J. H. (Rowntree): Studies of adrenal glands in health and disease. I. Diseases of adrenal glands as revealed in 25,000 autopsies 256
Claus, P. E.: cf. Guyer.....436
Cleghorn, R. A.: Effect of injections of extracts of adrenal cortex on development and sex functions of albino mouse.....144
Cleveland, R. (Wolfe): Cyclic histological variations in the anterior hypophysis of the sow (Sus scrofa) 644
— cf. Wolfe 157, 647
Cloney, Elizabeth: cf. Baird.....550
Close, H. G.: cf. Bishop.....152

Closs, K. (Loeb and MacKay): The effect of an acid extract of the anterior pituitary gland upon the iodine concentration of the blood and thyroid gland. 293
Cocchi, A.: The influence of the corpus luteum on the maternal instinct, experimental researches 745
Cockrill, J. R.: cf. Albright 302
Coco, R. M.: cf. Johnson 86
Coelho, E.: Acid-base equilibrium in thyroid disease 307
Cohen, M. B. (Rudolph and Rogoff): The output of epinephrine from the adrenal glands during anaphylactic shock 144
Cole, H. H. (Guilbert and Goss): Further consideration of the properties of the gonad-stimulating principle of mare serum. 285
— (Hart, Lyons and Catchpole): The development and hormonal content of fetal horse gonads 548
— (Miller): Artificial induction of ovulation and oestrum in the ewe during anoestrum. . 286
Cole, W. H. (Womack): Effect of certain extracts on basal metabolism of guinea pigs 307
Collazo, J. (Marañon, Roda and Torres): The action of adrenal cortex extracts on blood cholesterol 739
— cf. Marañon 393
Collier, W. D.: cf. Werner. . 291, 749
Collin. R.: The histological origin of the hormones of the posterior lobe; "Intermedian" 750
— (Drouet): Extracts of the posterior hypophyseal lobe and changes in weight in the frog 644
— — The anterior lobe of the pituitary and the reaction of the melanophores 644
Collip, J. B. (Browne and Thomson): Chemical nature of emmenin 71
— (Selye, Anderson and Thompson): Production of estrus; relationship between active principles of placenta and pregnancy blood and urine and those of the anterior pituitary 639
— cf. Anderson 291
— cf. Selye 237, 749
Combes, T. J. C.: Observations on human subject 5 years after splenectomy 762
Commins, W. D.: The effect of castration at various ages upon the adult weight of male albino rats 286
Cope, O.: cf. Albright 760
— cf. Churchill 761
Corey, E. L.: The effect of corticoadrenal extract injection on the oestrous cycle of the rat 144
Cosmulesco, I.: cf. Rathery 302
Courrier, R. (Gros): Experimental genital crises in new-born kittens 548
— (Kehl): Folliculin abortions in rabbits 745
— — Further work on pregnancy in rabbits 745
Courth, H.: Iodine metabolism of normal and thyroidectomized goats after potassium iodide and plant iodide feeding 450
Cowgill, G. R. (Palmier): Studies in the physiology of vitamines; the effect of experimentally induced hyperthyroidism on the vitamin B requirement of pigeons 307
Cramer, W.: Changes in the islets of Langerhans in pregnancy and other conditions ... 649
Csepai, K.: The iodine-x-ray treatment of Basedow's disease 308
Curtis, G. M. (Davis and Phillips): Significance of iodine content of human blood 658
Curutchet, J. L.: cf. Campos 433
Cushman, Beulah: Studies of visual fields in functional headaches of pituitary origin 551
Cuthbert, F. P.: cf. de Takats ... 760
Cutler, E. C.: cf. Levine 765
— cf. Zollinger 648
Cuyler, W. K.: cf. McCullagh 150
Czoniczer, G. (Kleiner): Anterior pituitary extracts in Graves' disease 434
Da Costa, Esther (Carlson): The effect of feeding desiccated thyroid upon the sexual maturation of the albino rat 308
— — The effect of feeding thyroid upon the sexual maturation of the albino rat 450
Daggs, R. G.: cf. Eaton 153
Dambrosi, R. G.: The pancreas and the vagi in muscle glycogen restorage after fatigue in cats. . 757
— The pancreas in muscle glycogen recovery after fatigue. . 757
— The vagi and splanchnic nerves in muscle glycogen restorage in dogs 757
— (Leloir): The adrenals in muscle glycogen recovery after fatigue 739
Damon, L. A.: Bilateral suprarenal hemorrhage and death in epilepsy 425
D'Amour, F. E.: cf. Dumont 206
D'Amour, M. C.: An attempt to duplicate certain hormone responses by means of drugs 235
— (Keller): Blood sugar studies following hypophysectomy and experimental lesions of hypothalamus 644

Dragstedt, L. R. (Risk and Johnson): The effect of the continuous intravenous injection of Ringer's solution on the blood chemistry of thyroparathyroidectomized dogs 654
Drouet, P. L.: cf. Collin.....644
Druckrey, H.: cf. Reiss.....440
Duff, G. L. (Bernstein): Addison's disease with so-called atrophy of the adrenal cortex..740
Dumont, Charlotte (D'Amour and Gustavson): Effect of introduction of blood from bred rabbits upon immature rabbits 206
Duncan, W. S.: Relationship of thyroid disease to chronic nonspecific arthritis 308
Dunhill, T. P.: cf. Elmslie.....160
Dye, J. A.: Adrenal cortical hormone and tissue respiration....544
Dyer, F. J.: Estimation of parathyroid hormone 302
— (van Dyke): The inhibition of estrus by extracts of the anterior lobe of the pituitary body 434
— — The inhibition of oestrous by extracts of the anterior lobe of the pituitary body.293
Danforth, C. H.: Genetic factors in the response of feather follicles to thyroxin and theelin...546
Dann, M. (Chambers and Lusk): Animal calorimetry; influence of phlorhizin glycosuria on the metabolism of dogs after thyroidectomy 308
Davis, B. L. (Hinsey and Markee): Constituents in normal urine producing hyperglycemia previously attributed to prolan...382
Davis, C. B.: cf. Curtis.....658
Davis, D.: cf. Blumgart....448, 693
Davis, J. E. (Hastings): The relationship of the adrenal and thyroid glands to excised muscle metabolism 543
Davison, C.: Xanthomatosis and the central nervous system....152
Davy, Leita: Complete recovery of gonadotropic substances from urine of pregnant women..... 1
Desaux, A. (Guillaumin): Changes in the interferometer readings (method of Hirsch) in the course of the menstrual cycle..742
Dauphinee, J. A.: cf. Elmslie....160
De Meio, R. H. (Lewis): Corticoadrenal hormone in urine.....634
— — Method for a biologic estimation of the adrenal cortical extract 276
Derick, C. L. (Newton, Schulz, Bowie and Pokorny): Spontaneous hyperinsulinism; report of a case of hyperinsulinism cured by surgical intervention.649
Deselin, L.: cf. Brouha.....638
Dick, G. F.: cf. Williams.....653
Dickie, Lois F. N.: cf. Thomnson 228, 664, 665
Döderlein, A.: cf. Borst.....285
Dohrn, M.: cf. Hohlweg.....751
Donelson, Eva: cf. Hunscher....428
van Dyke, H. B.: cf. D'Amour.. .....293, 434
Dykshorn, S. W.: cf. Riddle.155, 156

Eaton, A. G. (Daggs): Carbohydrate metabolism and specific dynamic action in partially hypophysectomized dogs 153
— (Murlin): The absorption of insulin from the gastro-intestinal tract; the effect of calcium lactate, sodium, bicarbonate and blood serum in depancreatized dogs.....443
Ebina, T.: The mechanism of the action of thyroxine in tissue metabolism 764
Edeiken, L.: Small doses of x-ray for amenorrhea and sterility...148
Ehrhardt, K.: Clinical and animal experiments on the melanophoric agent of the posterior pituitary lobe 434
— (Weigel): Investigations of corpus luteum hormone....745
Eisler, B.: cf. Schittenhelm.....315
Eitel, H. (Loeser): Relation of thyroid activity to the pituitary gland 434
— — Relationships between the anterior pituitary lobe, thyroid glands and the carbohydrate metabolism of the liver 434
Elek, L.: Influence of hormones on blood sugar regulation....650
Elkeles, A.: cf. Friedmann.....281
Elliott, A. H. (Nuzum): Urinary excretion of a depressor substance (Kallikrein of Frey and Kraut) in arterial hypertension 462
Ellison, E. T. (Wolfe): Effect of castration on anterior hypophysis of female albino rat.....555
Ellman, P.: Use of insulin in treatment of pulmonary tuberculosis 300
Elmer, A. W.: Iodine tolerance test for thyroid insufficiency...487
Elmslie, R. C. (Fraser, Dunhill, Vick, Harris and Dauphinee): Diagnosis and treatment of generalized osteitis fibrosa with hyperparathyroidism 160
Emery, F. E.: The anterior pituitary sex hormone in relation to the prolongation of estrous cycles and the production of a refractory condition of theelin..751
— The hypertrophy of the ovary in relation to the ovarian hormone 428
— (Atwell): Hypertrophy of the adrenal glands following administration of pituitary extract 740

Engelbach, W. (Schaefer and Brosius): Endocrine dwarfism ...387
Engle, E. T.: Biological difference in response of the female macacus monkey to extracts of the anterior pituitary and of human pregnancy urine 639
— Luteinization of ovary of monkey by means of combined use of anterior pituitary extract and an extract of pregnancy urine 505
Enzmann, E. V. (Saphir and Pincus): Delayed pregnancy in mice 286
Eppinger, E. C.: cf. Levine.....765
Eskin, J. A.: The influence of the adrenal on the metamorphosis of amphibians 276
Essex, H. E.: cf. Herrick.....310
Estrin, E.: cf. Asimov.....762, 763
Evans, E. I.: Diabetogenic principle of the anterior pituitary...435
— Initiation of copious milk secretion in virgin goats by anterior pituitary 435
Evans, H. M.: Present position of our knowledge of anterior pituitary function 435
— (Pencharz and Simpson): Maintenance and repair of reproductive system of hypophysectomized male rats by hypophyseal synergist, pregnancy-prolan and combinations thereof 607
— — Repair of reproductive system of hypophysectomized female rats by combinations of an hypophyseal extract (synergist) with pregnancy-prolan 601

Fancher, J. K.: Endocrine statistics from the Southeast.....221
Faure, S.: cf. Choay 639
Fauvet, E.: Hormones of posterior lobe of hypophysis and pregnancy toxicoses 746
Favilli, G.: Influence of some organ extracts on permeability to water of sea-urchin eggs (Arbacia Punctulata) 281
Fehr, A.: cf. Guyenot.....644
Fellenberg, T. (Gruter): Influence on the milk secretion of goats of extirpation of the thyroid 659
Fellner, O. O.: The uterus as an organ of internal secretion....548
Fenn, G. K.: cf. de Takats.....653
Ferguson, G. C.: cf. Best.....756
Ferguson, J.: Secretin: Its influence on amount of hemoglobin in circulating blood 188
Ferguson, R. S.: Pathologic physiology of teratoma testis.....746
Fevold, H. L. (Hisaw, Hellbaum and Hertz): Sex hormones of the anterior lobe of the hypophysis, further purification of a follicular-stimulating factor and the physiological effects on immature rats and rabbits 435
Field, Jean C.: cf. Morgan.....655
Figueroa-Casas, P.: Oxytocic factors in blood of pregnant women 746
Fineman, A. H.: Use of suprarenal cortex extract in treatment of bronchial asthma 425
Fink, E. B.: Gumma of the hypophysis and hypothalamus...751
Firor, W. M. (Reynolds): Experiments on hypophysectomized rabbits 153
— cf. Grollman 276, 634
— cf. Shumacker 676
Fischl, F.: cf. Reiss 440
Fisher, L. C. (Reimann): Effect of insulin on blood sugar of rabbits during infection 157
Flaum, E.: Parotid hypertrophy a sign of diabetes mellitus 443
Florentin, P.: Some remarks concerning the histogenesis of the mammalian thyroid 309
Fluhmann, C. F.: Biological characteristics of ovary-stimulating extracts made from blood of pregnant women 148
— Comparative studies of gonad-stimulating hormones; effect of prolonged injections in immature rats 746
— Comparative studies of gonad-stimulating hormones; influence of length of period of administration of certain extracts 428
— New procedure for demonstration of estrin in blood of women 705
Foncin, A. R.: Experimental cryptorchidism in guinea pigs..747
Fonio, A. (Scheurer): The effect of thyroxine and of iodine in a dosage analogous to the iodine content of thyroxine on some phases of metabolism on the blood, etc., in endemic cretins.451
Ford, F. A. (Mueller): A study of the estrus-producing hormone in the circulating blood of normal women 286
Foster, G. L. (Gutman and Gutman): Total and thyroxine iodine content of thyroid gland after injection of saline anterior pituitary extracts 451
Foster, M. A.: cf. Johnson..... 86
Foster, R. F.: cf. Wilder.....455
Foulger, J. H.: cf. Morris.....282
Frank, R. T.: cf. Spielman.....431
Fraser, F. R.: cf. Elmslie.....160
Frawley, J. T.: cf. McCullagh...150

Fredericq, H.: Contributions to study of tetany occurring at oestrus in thyroparathyroidectomized animals; action of the gonadotropic principle from the urine of pregnancy on tetany and blood calcium in dogs.....654
Freed, S. C.: Traumatic shock in adrenalectomized rats 276
Freeman, H. (Hoskins): Comparative sensitiveness of schizophrenic and normal subjects to glycerine extract of adrenal cortex 576
Freeman, N. E. (Morrison and Sawyer): The effect of dehydration on adrenal secretion and its relation to shock 425
Frei, W.: On the etiology of nymphomania of the cow.....149
Frieder, A.: cf. Herzfeld.....761
Friedman, A.: cf. Girard.....747
Friedman, Gertrude Sanders (Friedman): An examination of cerebrospinal fluid, by means of the uterine fistula, for the presence of the oxytocic factor of the posterior pituitary.....294
Friedman, H. H.: cf. Friedman..294
Friedman, M. H.: On the mechanism of ovulation in the rabbit; quantitative observations on the action of extracts of urine of pregnancy 747
— The production of functional corpora lutea unilaterally by the direct intrafollicular injection of extracts of urine of pregnancy 287
Friedemann, U. (Elkeles): Auxoneurotropic action of epinephrine and of solution of pituitary.281
Fukui, S. (Murata): The hormone of anterior lobe of hypophysis 294
Fuld, H.: cf. Thannhauser.....446
Funk, C. (Harrow): The male hormone; the effect of the male hormone and the anterior pituitary 287

Gabrielianz, A. G.: Organotherapy of mastodynia 287
Gaebler, O. H.: Some effects of anterior pituitary extracts on nitrogen metabolism water balance and energy metabolism...153
Gaetan, L.: cf. Marañon.....393
Gallagher, T. F. (Koch): Biochemical studies on male hormone as obtained from urine..107
Gann, E. L.: cf. Johnson..... 86
Gardner, W. U. (Turner): The function, assay and preparation of galactin, a lactation-stimulating hormone of the anterior pituitary and an investigation of the factors responsible for the control of normal lactation.436
Garra, A.: cf. Mussio-Fournier..656
Garrison, E. Alta: cf. Morgan... ..... 655, 656
Geiger, E.: Insulin and thermoregulation 443
Gellhorn, E. (Northup): The influence of hormones and drugs affecting the autonomic nervous system on intestinal absorption and permeability 154
Gibson, R. B.: Latent tolerance in diabetes mellitus 300
Gilchrist, J. A. (Alexander): Staphylococcic infections in diabetes 650
Gillum, F.: cf. Morgan.....656
Gilroy, E.: The effect of arginine upon the body weight of mice injected with thyroxine, and bearing the tumor M63...309
Ginsburg, S.: Masked thyrotoxicosis simulating primary neurosis.659
Girard, A. (Sandulesco and Fridenson): On the absorption, when given by mouth, of folliculin and its dihydrogenated derivative 747
Glimm, E. (Wadehan): The presence of the female sex hormone in urine 288
Glud, P. (Pedersen-Bjergaard and Portman): On the pregnancy reaction in mares 549
Goldberg, I.: Anterior pituitary extract and plasma proteins...436
Goldberg, M.: Treatment of pituitary infantilism with antuitrin 233
Goldberger, M. A.: cf. Spielman..431
Goldemberg, L.: The basal metabolic rate and the suspension stability of blood 765
— Therapeutic action of fluorides in exophthalmic goiter and hyperthyroidism: technic of fluoride treatment 309
Goldsworthy, Edith: cf. Greisheimer 444
Goldzieher, M. A.: Effects of interrenal function of fat metabolism and tissue respiration ...179
— (Sherman and Alperstein): Fat tolerance test in pituitary disease 505
Gomes da Costa, S. F. (Guedes): The sensitization to the action of x-ray of ulcerative skin cancer by insulin locally applied..650
Gondard, L.: Does denervation of the adrenal glands cure experimental pancreatic diabetes?...740
Goodwin, A. M.: cf. Abbott.....658
Goormaghtigh, N.: Temperature regulation and suprarenals. Morphologic study of activity of medulla of suprarenal 276
— The weight of the thyroid gland in the Belgian low-lands....659
Goss, H.: cf. Cole.....285
— cf. Guilbert 149

Gostimirovíc, D. (Kraemer): Treatment of disturbances of the estral cycle with sex hormones 549
— cf. Borst 285
Gott, R. J.: Hemochromatosis...742
Gotta, H.: cf. Yriart 454
Grab, H.: The occurrence of thyroid gland substances in the blood after the anterior pituitary has exerted its effect.....551
Gragert, O.: On the hormone therapy of oligo-hormonal secondary amenorrhea 149
Greene, C. H.: cf. Camp.....143
Greep, R.: Effect of luteinizing and follicular stimulating fractions of pituitary on the thyroid 436
Greisheimer, Esther M. (Goldsworthy and Thomas): High carbohydrate and high fat diets..444
Gresser, E. B.: Studies of retinopathies; diabetes mellitus 757
Grollman, A. (Firor): Observations on the hormone of the adrenal cortex 276
—— Studies on the adrenal; the preparation of an active extract of the hormone of the adrenal cortex.....634
— (Howard): The effects of adrenal cortex extract on the reproductive system 145
Gros, G.: cf. Courrier.....548
Gruter, F.: cf. Fellenberg.....659
Guedes, F. B.: cf. Gomes da Costa 650
Guerrero, I.: cf. Rossignoli.....314
Guilbert, H. R. (Goss): Some effect of restricted protein intake on the oestrous cycle and gestation in the rat 149
— cf. Cole 285
Guillaumin, C. O.: Method of recording and interpreting results derived from the sero-interferometer method of Hirsch applied to endocrine dystrophies 281
— cf. Desaux* 742
Guimarias, A.: cf. Athias.....547
Gustavson, R. G.: cf. Dumont....206
Gutman, A. B. (Sloan, Gutman and Palmer): Rôle of diiodotyrosine in hyperthyroidism; comparison of therapeutic effect of diiodotyrosine with inorganic iodine 451
— cf. Foster 451
Gutman, E. B.: cf. Foster.....451
— cf. Gutman 451
Guyenot, E. (Bartschi and Ponse): Sex antagonism and spontaneous feminization in male guinea pigs carrying ovarian grafts..640
—(Ponse, Fehr and Moszkowska): Action of alkaline extracts of anterior lobe on immature female guinea pigs..644
Guyer, M. F.: Heredity and the constitution of child.....742
— (Claus): Cellular constituents of the anterior hypophysis after uterine implants of carcinoma in rats 436

Haines, S. F.: cf. Rankin.....315
Halban, J.: The therapy of hemorrhages in the sexually mature woman 148
Hall, F. C. (Monroe): Thyroid gland deficiency in chronic arthritis 451
Hall, J. F.: cf. Sherwood.....431
Hamblen, E. C.: Human ovarian responses to extracts of pregnancy urine—preliminary report 640
Hamilton, A. S.: Effects of sodium bromide and other haloid salts upon weight and structure of thyroid gland in albino rat....170
Hamilton, B. (Schwartz): Rickets and hyperparathyroidism 654
Hampel, C. W.: cf. Ring.....159
Harned, B. K. (Nash): The protection of insulin by antiproteases, and its absorption from the intestine 157
Harris, C. F.: cf. Elmslie 160
Harris, S.: Hyperinsulinism, a definite disease entity; etiology, pathology, symptoms, diagnosis, prognosis and treatment of spontaneous insulogenic hypoglycemia (hyperinsulinism) ...758
Harrop, G. A. (Widenhorn and Weinstein): Metabolic investigations on the hormone of the adrenal cortex 544
Harrow, B.: cf. Funk.....287
Hart, E. B.: cf. Kozelka.....655
Hart, G. H.: cf. Cole.....548
Hartman, C. G.: Pelvic (rectal) palpation of the female monkey, with special reference to the ascertainment of ovulation time.747
Hartman, F. A.: Certain functions of the adrenal cortex....740
— (Lockwood and Brownell): Further studies on the adrenal cortex 145
Hartoch, W.: cf. Zondek.....300
Haslewood, G. A. D.: cf. Marrian.150
Hastings, A. B.: cf. Davis.....543
Haterius, H. O.: The relation of pregnancy cells in the pituitary of the rat to the reproductive cycle 288
Haupstein, P.: On the mechanism of action of the follicular hormone 640
Hawkins, J. O.: cf. Stanley 441
Hayaski, K.: Experimental erythropoiesis in the adrenal of splenectomized guinea pigs....277
Heaton, T. G.: The use of insulin as an aid in the treatment of pulmonary tuberculosis 650
Hechler, Ruth: cf. Lucke.....554

Heim, K.: On the biology of the mammary glands. A contribution to the question of the hormone of the anterior lobe of the pituitary 153
Heinbach, W. F.: A study of the number and location of the parathyroid glands in man.....654
Hellbaum, A.: cf. Fevold.....435
Hellbaum, A. A.: cf. Casida.....249
Heller, T.: Action of extract of posterior lobe of pituitary after intramuscular injection into cervix uteri 294
Hellwig, C. A.: Experimental colloid goiter 197
— The life line of the North American thyroid gland ...659
Hemmingsen, A. M.: The correlation between the blood-sugar fall and the initial blood-sugar in rabbits injected with insulin.650
Hermann, H. (Merklen, Santenoise and Vidacovitch): Pressure on the eyeball and the discharge of adrenaline 741
Herrick, J. F. (Essex, Mann and Baldes): The effect of feeding desiccated thyroid gland on the flow of blood in the femoral artery of the dog.....310
Hershey, J. M.: cf. Best.....756
Hertz, R.: cf. Fevold 435
Hertz, S. (Kranes): Exhaustion phenomenon in thyroid produced by pituitary treatment: histological study of rabbit's thyroid under varying degrees of anterior pituitary therapy..415
— — Parathyreotropic action of the anterior pituitary; histologic evidence in the rabbit 350
Herzfeld, E. (Frieder): Contribution to the knowledge of parathyroid activity 761
Hess Thaysen, T. E.: cf. Roholm.652
Hetényi, G.: Contributions on the physiology and pathology of the so-called kidney threshold (sugar threshold) in human beings 651
Heydemann, E. R.: cf. Lucke...554
Hick, F. K.: A suprarenalin-producing pheochromocytoma of the suprarenal gland 634
Hill, H. G.: cf. Broster.....275
Hills, M. J.: cf. Morgan.....656
Himsworth, H. P.: The activation of insulin 157
Hinglais, H.: cf. Brindeau.....292
Hinglais, M.: cf. Brindeau.....292
Hinsberg, K.: cf. Casas 300
Hinsey, J. C.: cf. Davis.....382
Hirsch-Hoffman, H. U.: Secretion of hormone of anterior lobe in urine in endocrine disturbances.552
— The influence of the hormone of the anterior lobe of the pituitary present in pregnancy urine on the ovaries of adult mice 437
Hisaw, F. L.: cf. Fevold.....435
Hochwald, A.: cf. Reiss.....440
Hoffman, F.: Isolation and demonstration of hormone of parathyroid in blood of pregnant women 446
— cf. Anselmino 762
Hogreve, F.: cf. Lendel.....282
Hohlweg, D. (Dohrn): Relation between the anterior lobe of the hypophysis and the gonads....751
— (Junkmann): The relationship of the anterior pituitary to the thyroid 552
Holten, C. (Schidt): Case of Addison's disease treated with Swingle and Pfiffner's extract of suprarenal cortex 277
Hoskins, R. G.: The tides of life: the endocrine glands in bodily adjustment 142
— cf. Freeman 576
Houssay, B. A.: Asthenia of hypophysectomized toads 437
— Hypophyses and thyroids. XIII. Thyroid of rats in parabiosis and injected with anterior pituitary extract 295
— Influence of pituitary on basal metabolism and on specific dynamic action 409
— Pituitary and metabolism....295
— (Artundo): Effect of anterior pituitary extract and specific dynamic action in thyroidectomized and hypophysectomized-thyroidectomized dogs.752
— — Effect of anterior pituitary lobe extract on basal metabolism of hypophysectomized and thyroidectomized dogs 752
— — Pituitary and thyroid activity in relation to basal metabolism 660
— (Biasotti): Hypophysis and pancreatic diabetes in batrachians and reptiles 553
— (Biasotti and Magdalena): Hypophysis and thyroid; action of anterior lobe extracts on the histology of the dogs' thyroid 645
— — Hypophysis and thyroid; hypophysis and compensatory hypertrophy of the thyroid 660
— — Pituitary and thyroid; effect of anterior pituitary lobe extract on microscopical aspect of thyroid.....310
— (Biasotti and Mazzocco): Action of anterior pituitary extract on blood iodine of thyroidectomized and hypophysectomized dogs 437
— — Hypophysis and thyroid action of anterior lobe extracts on the weight of the thyroid 645

Houssay, B. A. (Biasotti and Mazzocco): Pituitary and thyroid VIII. Anterior pituitary lobe extract on weight of thyroid...294
— (Biasotti, di Benedetto and Rietti): Anterior pituitary extract in phlorizin diabetes.438
— — Diabetogenic activity of anterior pituitary extracts..437
— — Diabetic effects of extract of anterior lobe of hypophysis in dogs.....553
— (di Benedetto): Anterior pituitary extract and hyperglycemia produced by morphine and adrenaline 645
— — Rôle of the hypophysis in adrenaline and morphin hyperglycemia 295
— (di Benedetto and Mazzocco): Hypophysis and glycogen in toads 552
— (Mazzocco and Biasotti): Hypophysis and thyroid; effect of anterior lobe extract on blood iodine 295
— (Riette): Hypophysis and thyroid; extracts of the anterior lobe of the hypophysis and susceptibility to lack of oxygen 660
— (Rubio): Functions of the grafted gall bladder. Duodenal cholecystokinetic hormone 282
Howard, Evelyn: cf. Grollman...145
Hubble, D.: Influence of endocrine in blood disorders.....636
Huber, W.: cf. Paal.....314
Hückel, R.: cf. Lucke.....439
Hunscher, Helen A. (Donelson, Nims, Kenyon and Macy): Metabolism of women during the reproductive cycle; nitrogen utilization 428
Hunt. H. M.: cf. Joslin.....444
Hurthle, R.: Hypophyseal cachexia 553
Hurxthal, L. M.: Blood cholesterol in thyroid disease; effect of treatment 660
Huszak, St.: cf. Annau.....739
Hutton, J. H.: cf. Nerancy.....642

Imuro, S. (Murata): Amount of so-called hypophysis hormone in blood and urine in pregnancy..295
Ito, Y.: cf. Ogata.....289
Iwanow, G.: The chromaffine and interrenal system of man.....277

Jakobson, B. M.: The effect of insulin and adrenaline on the excretion of nitrogen and sulfur..651
Jamieson, H. C.: The high carbohydrate low fat diet for diabetic children 651
Jaso-Roldan, L.: cf. Aschner....755
Jenkins, R. L.: Etiology of mongolism 636
John, H. J.: Glucose tolerance studies in children and adolescents 75
Johnson, Anna A.: cf. Risk.....654
Johnson, G. E. (Gann, Foster and Coco): Effect of daily heteropituitary implants into adult but sexually inactive male ground squirrels 86
Johnston, R. L.: Studies in physiology of prostate gland.....123
Jones, Mildred (Barnes): The thyroxine content of thyroglobulin.310
de Jongh, S. E. (Mulder): Masculinization of the external genitalia of female guinea pigs by injection of male hormone.....428
Jordon, W. R.: Epilepsy and convulsions in diabetes 651
— Neurological manifestations of hypoglycemia 758
Josefson, A.: Nervous organic disease 426
Joslin, E. P.: Fat and the diabetic.758
— (Root, White, Marble and Hunt): Diabetic coma 444
Josserand, A.: cf. Arloing.....633
Junkmann, K.: cf. Hohlweg.....552

Kaiwa, T.: The effect of thyroidectomy and adrenalectomy on the basal metabolic rate of the rabbit 311
Karnicki, W.: The influence of the endocrine glands on the development and maintenance of experimental cancer 742
Karr, W. G. (Scull and Petty): Insulin resistance and sensitivity 652
Kaufman, L.: Experiments on the effect of injections of extracts from aged and embryonic animals on the growth of mice...637
Kehl, R.: cf. Courrier 745
Keller, A. D.: cf. D'Amour.....644
Kelly, G. L.: Simple test for pregnancy using immature female albino rats; premature establishment of vaginal orifice by intraperitoneal injections of urine of pregnant women 288
— The effect of anterior hypophysis on conception and pregnancy 428
Kemp, T.: Inheritance of sporadic goiter 660
— (Pedersen-Bjergaard): On the absorption and elimination of folliculin in man.....747
Kemp, W. N.: Hyperemesis gravidarium treated as a temporary adrenal cortex insufficiency....544
— The stillbirth problem in relation to iodine insufficiency..661
Kennedy, W. P.: Quantitative variation of the anterior pituitary hormone, "APH-B," in the blood during pregnancy 553
— The mouse unit of anterior pituitary hormone B 553

Kennedy, H. S.: cf. Anderson.... .....143, 744
Kenyon, Fanny: cf. Hunscher...428
Kenyon, Josephine H.: Hypopituitary type of obesity treated without glandular medication..154
Kepler, E. J. (Barnes): Congestive heart failure and hypertrophy in hyperthyroidism; a clinical and pathological study in 178 fatal cases .....
Kincov, J. (Zillessen and Rowntree): Studies of the adrenal glands in health and disease. II. Effects of an excess of cortical hormone in Addison's disease..361
King, A. G.: Uterine reactions to sex hormones in the immature guinea pig 539
Klein, M.: The relations between the gravid uterus and the corpus luteum in rabbits during the latter half of pregnancy.....747
Kleiner, G.: cf. Czoniczer.....434
Knab, F.: Treatment of hemorrhages of ovarian origin by means of hormone of corpus luteum 748
Koch, F. C.: cf. Gallagher.....107
Koehler, Gertrude: cf. Zondek...442
Koh, M. L.: Method of estimating functional activity of thyroid by means of urine or serum and studying relationship between thyroid and other endocrine glands 311
v. Kowkas, E.: cf. Verzár.....297
Kolodner, L. J.: cf. Rubinstein..754
Kosaka, Y.: Quantitative studies on the cortex and medulla of the suprarenal gland in the adult guinea pig 277
Kozelka, F. L. (Hart, Bohstedt): Growth, reproduction and lactation in the absence of the parathyroid glands 655
Kovacs, F.: The pathology of hirsutism and virility 429
Kraemer, G. O.: cf. Gostimirovic.549
Kraft, Ruth, M.: The effects of the gonadal-stimulating hormone of the anterior pituitary on the voluntary activity, the age of maturity and the size of the litter in immature female albino rats 438
Kranes, A.: cf. Hertz.....350, 415
Kraul, L.: The influence of hormonal substances on the function of the anterior lobe of the pituitary and the practical importance of this 752
Krčma, A.: cf. Löw.....301
Kroc, R. L.: cf. Martin.....145
Krock, F.: cf. Taylor.....431
Krogh, M. (Okkels): Is the thyroid-stimulating hormone of the anterior lobe of the hypophysis eliminated by the kidney.....645
Krohn, H.: cf. Zondek.....299
Kubo, S.: Influence of adrenalectomy on fat content of diuerent organs and influence of sulfur on fat content of adrenalectomized animals 277
Kugelmann, B.: The relations between insulin and adrenaline in humans 301
Kühmau, J.: cf. Schmitz.....741
Kun, H.: cf. Steinach.....290
Kurzrok, R. (Bates, Riddle and Miller): Clinical use of prolactin 18
Kustner, H.: The treatment of eclampsia and pre-eclampsia with thyroxine 312

La Barre, J. (Lorthioir): Insulin secretion after radiation of the pancreatic region 759
— cf. Zunz 636
Labbé, M. (Azérad and Solomon): Condition of vegetative nervous system in exophthalmic goiter and in Basedowoid sympathetic syndrome 312
Lanari, A.: cf. Campos.....433
Lande, H.: Uncontrollable causes of death in diabetic coma.....158
Landon, J. F.: Parathyroidectomy in generalized osteitis fibrosa cystica; report of a case in a child 2½ years of age.....761
Langsdorf, O.: Circulatory aspects following experimental suprarenalectomy 634
Larrosa, Helguera, R. A.: cf. Mussio Fournier 527, 533
Lee, M. O. (Schaffer): The effect of anterior pituitary growth hormone on the composition of growth, and on ash, nitrogen and energy balances in rats under a paired-feeding regimen..154
Leet, N. B.: cf. Lisser.....333
Lehnherr, E. R.: Arteriosclerosis and diabetes mellitus 759
Leland, J. P.: cf. Palmer.....314
Lelkes, Z.: On the iodine content of the thyroid gland in the human foetus, new born and suckling 661
Leloir, L. F.: cf. Dambrosi.....739
Lendel, E. (Hogreve): Correlation of five hormone organs; hypophysis, thyroid, thymus, testes and suprarenal, in normal man and domestic animals, by means of interferometric method of Abderhalden reaction.....282
Lengyel, L.: cf. von Arnay.....275
Leonard, S. L.: Differential effect of prolan in decreasing the potency of the hypophysis in normal and castrate rats.....640
— Increased stimulation of immature rat ovaries by combined injections of prolan and hypophyseal sex hormone.....429

Leonard, S. L.: cf. Main.....629
— cf. Smith 441
— cf. White 298
Lerman, J.: Lymphoma of the thyroid; report of two cases...452
— (Means): Cardiovascular symptomatology in exophthalmic goiter 661
— (Salter): Calorigenic action of thyroid and some of its active constituents 317
— cf. Ayer 701
Letter: Action of the posterior lobe of the hypophysis in headache 295
Leulier, A. (Revol): Chemistry of adrenals of mammals. Comparative study of medulla and cortex 278
Levine, S. A. (Cutler and Eppinger): Thyroidectomy in the treatment of advanced congestive heart failure and angina pectoris 765
Lewis, J. T. (Turcatti): Adrenals and pancreatic diabetes 652
— cf. De Meio 276, 634
Lin, K. H. (Tsai and Wan): Oestrous rhythm of vegetarian and omnivorous rats 288
Lipschütz, A.: Further studies on the coefficient of luteinization..752
— Masculinization in guinea pigs by partial resection of the ovary 748
— Pigmentation of the mammary region of the hyperfeminized male guinea pig 288
— The coefficient of luteinization, functional measure of the anterior lobe of the hypophysis 296
— The experimental production of sexual characteristics in mammals 748
— (Reyes): A specific sex difference in the anterior lobe of the hypophysis in the rat...645
— — Sex specific differences in the behavior of the anterior lobe of the hypophysis in the rat.....296
— — The capacity for stimulating the formation of the corpora lutea found in the hypophyses of young and old female rats 296
— cf. Cadiz 745
Lisser, H. (Taylor and Leet): Adrenal cortical therapy of Addison's disease 333
Lockwood, J. E.: cf. Hartman...145
Loeb, L.: Anterior pituitary hormone acting on the ovary and differences in the reactions in different species 752
— Effects of different anterior pituitaries and human pregnancy urine on rat sex organs 641
— cf. Closs 293
Loeser, A.: The preparation of thyreotropic extracts of the anterior lobe 645
— The skin as a hormone bearer during pregnancy 429
— cf. Eitel 434
London correspondent: An international standard for the estrus-producing hormone 149
London, E. S.: Dynamics of internal secretions. I. Methods...301
— Dynamics of internal secretions. III. Internal and external secretions 301
Long, J. A.: cf. Pencharz.....646
Long, J. H.: cf. Novak.....642
Long, M. L. (Bischoff): A carbohydrate balance sheet for the adrenalinized fasting rat sacrificed in the recovery period....635
— cf. Bischoff.....635
Loos, H. O. (Rittmann): Suprarenal cortex and sexual development 741
Lorthioir, P.: cf. La Barre.....759
Löw, A. (Krčma): Insulin and liver fat 301
Lower, N. E.: The endocrine influence on the male sex organs.429
Lucarelli, G.: The action of the pituitary sex hormone on some endocrine glands (pancreas, adrenals, hypophysis, thyroid) after ligature of the deferen vessels 426
— The action of the pituitary sex hormone on the testicles after ligature of the vas deferens 753
Lucas, W. P. (Pryor): The body build factor in the basal metabolism in children.....637
Lucke, H. (Heydemann and Hechler): A specific hormone of carbohydrate metabolism antagonistic to insulin found in the anterior hypophysis 554
— (Hückel): The effect of extracts of the anterior pituitary lobe on growth 439
Lueders, C. W.: Insulin therapy in certain disorders of nutrition.444
Lund, S. E. T.: Mongolism in monozygotic twins 637
Lusk, G.: cf. Dann.....308
Lyons, W. R.: cf. Chaikoff.....757
— cf. Cole 548

Macdonald, A. D.: The action of pituitary extracts on the kidney.554
Macdonnell, P. M.: A case of glycosuria, simulating cerebral thrombosis; post-mortem diagnosis—brain tumor 652
Machii, H.: cf. Mauri.....278
MacKay, E.: cf. Closs.....293
Macleod, J. J. R.: The control of carbohydrate metabolism 445
Macy, Icie G.: cf. Hunscher.....428
Madhava, K. K.: cf. McCarrison.453

Magdalena, A.: Hypophysis and thyroid; action of extirpation and implantation of the hypophysis on the thyroid of B. arenarum 438
— Hypophysis and thyroid; effect of ablation or implantation of the thyroid on the hypophysis of toads 662
— cf. Houssay.....310, 645, 660
Main, R. J. (Leonard): Nature of gonadotropic hormone found in urine in case of teratoma testis.629
— cf. Ware 432
Mandel, F. (Uebelhör): Parathyroid hormone-osteitis fibrosa-kidney stone 160
Mandelshtam, A. E. (Chaykovisky): Hormonal sterilization of female organism 639
Mann, F. C.: cf. Herrick.....310
Marañon, G. (Collazo, Garton and Roda): Action of adrenal cortical hormone on elimination of cholesterol by bile 393
— (Salas and Arguelles): Digestive symptoms in chronic suprarenal insufficiency (Addison's disease) 497
— cf. Collazo 739
Marble, A.: cf. Joslin 444
Maresh, F.: cf. Martin.....278, 544
Marenzi, A. D.: Phosphocreatine and glutathione in muscle of hypophysectomized toads 646
Markee, J. E.: cf. Davis.....382
Marrian, G. F. (Haslewood): The chemistry of oestrin; mechanism of conversion of trihydroxy-oestrin into ketohydroxyoestrin.150
Martin, Carol: cf. Paul.....158
Martin, S. J. (Kroc): Effect of cortical extracts on the oestrual cycle of completely suprarenalectomized rats 145
— (Maresh): Temperature studies in normal and suprarenalectomized rats 278, 544
Martinez de Hoz, R.: cf. Masciottra 641
Marui, E. (Machii): Experimental investigation of action of adrenaline and destruction of same in bodies of normal, starved and phosphorous-poisoned rabbits with special regard to adrenaline poisoning by disturbance of liver function..278
Masciottra, R. L. (Martinez de Hoz): New test for diagnosis of pregnancy; hormonal hypercholesterolemia 641
Mathieu, F. (Barnes): Fate of the thyroid hormone in experimental hyperthyroidism 313
Maveroff, H.: Anterior pituitary extract and blood glutathione..439
— Hypophysis and blood glutathione 753
Mavromati, L.: The influence of the uterus on the secretion of folliculin by the ovary.....642
Maxwell, L. C. (Bischoff): Hormones in cancer; the effect of glandular extirpation upon resistance to tumor tissue grafts.743
— cf. Bischoff 742
Mayer, A.: Studies on the gaseous metabolism of rabbits following injections of the gonadotrophic principle of the urine of pregnant women 642
Mayer, Laurence H. (Welton): What we are and why.....423
Mayer, L. L. (Rony): Visual fields, blind spots and the optic disc in endocrine diseases 282
Mazzocco, P.: Specific dynamic action in fasting hypophysectomized dogs after lesion of tuber cinereum 439
— cf. Houssay.294, 295, 437, 552, 645
McCarrison, R.: Effect of sunlight and darkness on the thyroid gland 452
— (Madhava): The effect of insanitary condition on the thyroid gland and other organs of the body 453
McCrie, J. G. (Mears and Millar): A case of Addison's disease treated with cortical suprarenal extract 145
McCullagh, D. R. (Cuyler and Frawley): The origin of the comb-growth promoting substance in male urine 150
McCullagh, E. P.: Diagnosis of hypogonadism in the male....289
McHenry, E. W.: cf. Best.....547
McLean, D.: Further observations on testicular extract and its effect upon tissue permeability..150
McManus, Mary: cf. Rowe.....759
McQuarrie, I.: cf. Thompson....156
Means, J. H.: The diagnostic use of iodine in thyrotoxicosis.....765
— cf. Ayer 701
— cf. Lerman 661
Mears, J. M.: cf. McCrie.....145
Mecz, M.: cf. Rotter.....315
Medvedeva, A.: Specificity of hypoglycemia hormone of suprarenal gland 279
Meltzer, Sara: cf. Abbott.....658
Mendel, L. B.: cf. Reed.....150
Mengert, W. F.: Periodicals on endocrinology of sex.....421
— The relation of maternal metabolism to infant birth weight 453
Menninger, W. C.: Psychological picture of case of Laurence-Moon-Biedl syndrome 583
Merklen, L.: cf. Hermann.....741
Meyer, E.: Constitution of 3254 Freiburg students, including the size of thyroid gland.....313
Mikula, M.: A rare case of polydactylism 155
Miletzkaja, S.: cf. Asimov.....762
Millar, W. G.: cf. McCrie.....145
Miller, C. O.: cf. Siehrs.....147
Miller, E. G.: cf. Kurzrok..... 18

Miller, R. F.: cf. Cole.....286
Miller, R. H.: Lingual goiter....453
Mills, Sylvia M.: Evidence for a neurohumoral control of fish melanophores 547
Minot, A. S.: cf. Bryan.....159
Mittelmann, Bela: Psychogenic factors and psychotherapy in hyperthyreosis and rapid heart imbalance 313
Miwa, T.: The hormone of the spleen 447
Modell, W.: Observations on the structure of the blood vessels within the thyroid gland of the dog 662
Monroe, R. T.: cf. Hall.....451
Morato, J. X.: Cellular development and secretory phenomena in the anterior lobe of the hypophysis studied by the silver impregnation method. Further results of the application of silver staining to the study of the hypophysis 646
Morel, A.: cf. Arloing.....633
— (Field): Effect of diet on response to parathyroid extract and vitamin D; the relation of calcium and phosphorus of the diet to response to parathyroid extract in rats.655
— (Garrison): The effect of diet on response to parathyroid extract and vitamin D; the effect of high calcium low phosphorus diets in dogs...655
— (Garrison and Hills): The effect of diet on response to parathyroid extract and vitamin D; the effect of low calcium-high phosphorus diets in dogs 656
— (Garrison, Gillum and Hills): Effect of diet on response to parathyroid extract and vitamin D; the effect of diets of normal calcium and phosphorus content in dogs.....656
Morison, R. S.: cf. Freeman.....425
— Erythremia; therapeutic suggestion 426
— (Schiff, Foulger, Rich and Sherman): Observations on hematopoietic hormone (addisin) in pernicious anemia.282
Mortimer, H.: cf. Rowe..... 20
Mosinger, M.: cf. Roussy...647, 754
Moszkowska, A.: cf. Guyenot....644
Mueller, S. C.: cf. Ford.....286
Mulder, J. D.: cf. de Jongh.....428
Mulier, H.: cf. Topper.....665
Muñoz, J. M.: Anterior pituitary lobe extract and blood lipids...439
Murphy, D. P. (de Renyi): Sex determination of Dorn and Sugarman 521
Murata, M.: cf. Fukui.....294
— cf. Iimuro 295
— cf. Ueno 297
Murlin, J. R.: cf. Eaton.....443
Murphy, D. P. (Shoemaker and Rea): Menstrual response to luteinizing extract of pregnancy urine 203
Murray, M. M.: The antagonistic effect of alcohol on pituitary hyperglycaemia 554
Murray-Lyon, R. M.: The symptomatology of diabetes mellitus; an analysis of 1700 cases.....759
Musser, J. H. (Wright): Hypertension, obesity and hyperglycemia 445
Mussio-Fournier, J. C. (Garra and Castiglioni): A case of parathyroid tetany with normal chronaxie and gastric spasms..656
— (Larrosa Helguera): Optic nerve and myxedema 527
— (Castiglioni and Andio): Familial infantilism due to hypophyseal and thyroid insufficiency 533

Nakamura, U.: Experimental study of thyroid function during pregnancy, parturition and puerperium; on metabolism of iodine during pregnancy, parturition and puerperium 313
Nash, T. P.: cf. Harned.....157
Nelson, W. O.: Studies on the physiology of lactation. III. The reciprocal hypophyseal-ovarian relationship as a factor in control of lactation 33
— (Smelser): Studies on the physiology of lactation; lactation in the male guinea pig and its bearing on the corpus luteum problem 289
— cf. Barnes 649
Nerancy, J. T. (Steinberg and Hutton): Ovarian insufficiency and mental disorders 642
Netter, R.: cf. Bailly.....739
Neumann, H. O.: Experimental studies on the problem of sex inversion; a contribution on the question of antihormonal sterilization of male animals.....150
Newton, F. C.: cf. Derick.....649
Nilus, F.: Three cases of sclerotic blue and the endocrines 427
Nims, Betty: cf. Hunscher.....428
Nitzescu, I. I. (Canciovici): Insulin and the protein equilibrium of the blood serum.....652
Noble, E. (Ronald): Childhood myxedema 662
Noble, G. K. (Bradley): The relation of the thyroid and the hypophysis to the molting process in the lizard 743
Noether, P.: Biological evaluation of the colloid of beef hypophysis 296
North, J. P.: The use of continuous venoclysis of glucose after thyroid operations 453
Northup, D. W.: cf. Gellhorn ...154

Notkin, J.: A clinical study of psychoses associated with various types of endocrinopathy...283
Novak, E. (Long): Ovarian tumors associated with secondary sex changes; granulosa cell carcinoma and arrhenoblastoma..642
Novelli, A.: Posterior hypophyseal extract and imbibition in Batracians 646
— Posterior pituitary lobe and imbibition in batrachians 439
— Sexual activity of anterior pituitary lobe in female toads...296
Nowinski, V. W.: Relation between thymocrescin and thyroxine in the growth of animals 657
Nuzum, F. R.: cf. Elliott.....462

Oberdisse, K.: Metabolic studies on the site of action of thyroid.314
Oefelein, F. (Trautwein): Catalase studies in adrenalectomized guinea pigs and in Addison's disease 545
— — Studies on adrenalectomized guinea pigs 545
Offergeld, H.: The effect of follicular hormone on the untimely secretion of milk.....155
Ogata, A. (Ito): Male hormone. I. The hormone in the urine of males 289
Ohmi, F.: Again on the hypoglycemic ability of insulin upon rabbits doubly suprarenalectomized or splanchnicotomized..445
Okkels, H.: cf. Krogh 645
Oliver, Marguerite: cf. Scott....546
Oliver, Mary: cf. Scott.....546
Ornstein, I.: cf. Parhon 315
Ortenberg, S.: Parathyroid dysfunction; report of case treated with parathormone and irradiated ergosterol 657
österreicher, W.: Increased excretion of anterior pituitary lobe hormone "prolan" in the urine during the involuntional period and senility 554
Overholser, M. D. (Allen): Ovarian hormone and traumatic stimulation of monkey's cervix to a condition resembling early cancer 549

Paal, H. (Huber): Studies on Reid-Hunt reaction. IV. Dependence of content of active substance in thyroid glands upon alimentary and hormonal factors 314
Packard, M. (Wechsler): Chronic adrenal insufficiency: an hitherto undescribed syndrome: with case report 146
Palmer, W. W. (Leland): Observations of Morch's method for standardization of thyroid gland preparation 314
— cf. Gutman 451
Palmier, M. L.: cf. Cowgill.....307
Papanicolaou, G. N.: The sexual cycle in the human female as revealed by vaginal smears.....550
Parhon, C. I. (Cernautzeanu-Ornstein): Influence of extirpation of one external parathyroid on the lipoid contents of the corresponding undisturbed gland.657
— (Ornstein): Influence of thyroxine on cholesterolemia and lipemia 315
Parker, G. H. (Porter): The control of the dermal melanophores in elasmobranch fish.....753
Patton, Helen: cf. Starr.....113
Paul, W. D. (Clark and Martin): Hyperglycemia, glycosuria and the respiratory quotients as the result of insulinization of non-diabetics 158
Pavlovic, R. A. (Tihomirov): Morphological changes in the parathyroid glands of rabbits during poisoning with sodium fluoride 657
Pedersen-Bjergaard, K.: cf. Glud.549
— cf. Kemp 747
Pemberton, J. de J.: cf. Beaver..763
— cf. Wilder 455
Pencharz, R. I. (Long): Hypophysectomy in the pregnant rat.646
— cf. Evans 601, 607
Peter, H. (Rea and Visscher): The influence of calcium salts and parathyroid extract upon the energy liberation and efficiency of the heart 303
Petty, O. H.: cf. Karr.....652
Phillips, F. J.: cf. Curtis.....658
Pighini, G.: Pituitary hormones and the male genital organs...440
Pincus, G. (White): On the inheritance of diabetes mellitus; an analysis of 675 family histories 159
— cf. Enzmann 286
Pokorny, N.: cf. Derick.....649
Ponse, K.: cf. Guyenot.....640, 644
Porter, H.: cf. Parker.....753
Portman, K.: cf. Glud.....649
Prather, G. C.: The use of cortin following removal of a large adrenal tumor 425
Pratt, J. P.: Human corpus luteum and progestin 667
— Quantitative hormone requirements 211
Pryor, H. B.: cf. Lucas.....637
Pugsley, L. I.: The effect of parathyroid hormone and irradiated ergosterol on calcium and phosphorous metabolism in the rat.303
— (Selye): The histological changes in the bone responsible for the action of parathyroid hormone on the calcium metabolism of the rat.762
— cf. Thomson.....304
Putnam, T. J.: The present status of diseases of the hypophysis..754

Räihä, C. E. (Uotila): Has insulin an effect on the thyroid gland? 663
Rankin, E. W. (Haines): The diagnosis and treatment of atypical hyperthyroidism 315
Raposo, L.: Mechanism of pulmonary oedema following adrenine injections 635
Rapport, D.: cf. Canzanelli 307
Rasmussen, A. T.: Percentage of different types of cells in anterior lobe in adult human female. 754
Rathery, F. (Cosmulesco): Variations in free and combined sugar in diabetics following ingestion of glucose with or without insulin 302
Rea, C. E.: cf. Peter 303
Rea, M.: cf. Murphy 203
Reed, C. I.: Further studies on the physiological action of irradiated ergosterol 303
Reed, L. L. (Anderson and Mendel): Factors influencing the distribution and character of adipose tissue in the rat 150
Regan, J. F. (Barnes): The effect of previous hypophysectomy upon the diabetes resulting from pancreatectomy 159
— cf. Barnes 649
Reilly, W. A.: Some endocrine observations on advanced ossification in children 117
Reimann, H. A.: cf. Fisher 157
Reiss, M. (Druckery and Fischl): The energy basis of endocrine action; the metabolism of the testicle under the influence of the sexual hormone of the anterior lobe of the hypophysis 440
— (Hochwald and Druckrey): The rôle of growth hormone in the metabolism of liver and kidney 440
Remen, L.: Creatinuria and ovarian function 430
de Renyi, G. S.: cf. Murphy 521
Revol, L.: cf. Leulier 278
Reyes, G.: cf. Lipschütz 296, 645
Reynolds, S. R. M. (Allen): The action of corpus luteum extracts containing progestin on urine motility in the unanesthetized rabbit 289
— cf. Firor 153
Rich, M. L.: cf. Morris 282
Richter, C. P.: Cyclical phenomena produced in rats by section of the pituitary stalk and their possible relation to pseudopregnancy 647
Riddle, O.: Differentiating some functions of the anterior pituitary hormones 440
— (Bates and Dykshorn): The preparation, identification and assay of prolactin—a hormone of the anterior pituitary 155
Riddle, O. (Bates and Dykshorn): Thyroid hyperthrophy as a response to the gonad-stimulating hormone of the pituitary 156
— (Smith and Benedict): Seasonal, endocrine and temperature factors which determine percentage metabolism per degree of temperature change 283
— cf. Kurzrok 18
Rietti, C. T.: Ketosis in the pancreatic and phlorrhizin diabetes of hypophysectomized dogs 554
— cf. Houssay 437, 438, 553, 660
Rigoletti, L.: cf. Battistini 756
Ring, G. C. (Hampel): Effects of adrenal medulla and thyroid on the respiratory metabolism of pancreatic diabetes 159
Riseman, J. E. F.: cf. Blumgart. 448
Risk, R. R.: cf. Dragstedt 654
Rittmann, R.: cf. Loos 741
Robbins, J. H.: Use of cortin in a case of acute hyposuprarenalism occurring as a sequela of acute streptococcic sore throat 279
Robinson, M. H. B. (Thompson): The effect on the body temperature of animals of injection of an extract of parathyroid glands. 303
Robson, J. M.: The reactivity and activity of the human uterus at various stages of pregnancy and parturition 748
Rock, J.: Clinical trials with the so-called female sex hormone .. 430
— cf. Smith 431
Roda, E.: cf. Collazo 739
— cf. Marañon 393
Rogoff, J. M.: Experimental Chronic adrenal insufficiency (Addison's disease) in animals. 146
— cf. Cohen 144
Roholm, K. (Hess Thaysen): Hypoglycemic symptoms in diabetes; effect of intravenous injection of insulin 652
Ronald, A.: cf. Noble 662
Rony, H. R.: cf. Mayer 282
Root, H. F.: New cases of combined pernicious anemia and diabetes 445
— cf. Joslin 444
Rosenblueth, A. (Cannon): Some circulatory phenomena disclosed by ergotoxine 146
Rossignoli, J. J. (di Benedetto, Guerrero and di Benedetto): Physico-chemical changes in plasma of thyroidectomized dogs 314
Rotter, G. (Mecz): Standardization of thyroid preparations ... 315
Roussy, G. (Mosinger): Anatomical connections between the hypothalamus and the hypophysis 647
— — The indirect endocrine relationship between hypophysis and tuber cinereum .. 754

Rowe, A. W. (McManus): Metabolism in pregnancy; blood sugar changes during delivery. 759
— (Mortimer): Note on acromegaly with report of a case.... 20
Rowntree, L. G.: cf. Clark.....256
— cf. Kincov 361
Rubenstein, H. S.: Production of testicular descent with water-soluble (anterior pituitary-like) fraction of pregnancy urine ...475
— (Kolodner): The effect of the growth hormone on body and tail lengths 754
Rubio, H. H.: cf. Houssay.....282
Rudolph, J. A.: cf. Cohen.....144
Rudy, A.: The relation of the blood sugar to the symptoms of the insulin reaction; with a discussion of the mechanism of hypoglycemia 759

Salas, P.: cf. Marañon 497
Salter, W. T.: cf. Lerman.....317
Samarajew, W. N.: The mitogenetic rays of the blood in artificial hyperthyroidism and Basedow's disease 315
Sammartino, R.: cf. Schteingart. 453
Sand, Knud P.: The physiology of the testes 142
Sandulesco, G.: cf. Girard.....747
Santenoise, D.: cf. Hermann....741
Saphir, N. R.: cf. Enzmann.....286
Saphir, W.: Anterior pituitary hormone and tumor growth....191
— Concerning function of pineal body 625
Sasaki, K. J.: Relationship between internal secretions and sodium chloride content of bile. 283
Savage, M.: cf. Sherwood.....431
Sawyer, E. M. Mack: cf. Freeman. 425
Sawyer, Margaret E.: Eye reactions in pancreatic diabetes....652
Schaefer, R. L.: cf. Engelbach...387
Schaefer, W. H.: Hypophysectomy and thyroidectomy of snakes 453
Schaffer, N. K.: cf. Lee.....154
Schechter, M.: Cyanogen metabolism; thyroid gland activity and lack of oxygen.....663
Scherer, I. R.: cf. Allan.....157
Schereschewsky, N. A.: The adrenal-genital syndrome 279
Scheurer, G.: cf. Fonio.....451
Schick, B. (Topper): Lowered basal metabolism in conditions characterized by slow pulse rate. 637
Schidt, E.: cf. Holten.....277
Schiff, L.: cf. Morris.....282
Schittenhelm, A. (Eisler): Therapeutic experiments with hypophyseal hormone influencing thyroid 315
Schmitz, E. (Kühnau): The internal secretfon of the adrenal cortex 741
Schneider, E. (Widmann): Clinical and experimental studies of goiter problem and of exophthalmic goiter 664
Schockaert, J. A.: On the lack of identity between prolan and the gonadotropic hormone of the anterior lobe of the hypophysis. 755
Schrive, I. (Zwarenstein): Influence of gonads on protein metabolism; urinary creatinine after castration 290
Schteingart, M. (Sammartino): Action of fluorine on histological aspect of thyroid.....453
— cf. Castex 307
Schube, P. G.: Encephalography in abnormal mental states with diabetes insipidus 647
Schulz, R. Z.: cf. Derick.....649
Schwarcz, R.: A new pregnancy test; the Friedmann reaction on the blood plasma 749
Schwartz, C.: cf. Hamilton.....654
Schwarz, H. (Topper): Cholesterol partitions of the blood in myxedema (cretinism) 665
Scott, E. (Oliver and Oliver): Sympathetic tumors of the adrenal medulla 546
Scott, J. W.: cf. Cantor.....341
Scull, C. W.: cf. Karr.....652
Seekles, L. (Sjollema and Van der Kaay): Changes in the composition of the blood and in the tone of the vegetative nervous system in cows during pregnancy and parturition 290
Selye, H.: Action of parathyroid hormone on the epiphyseal junction of the young rat.....303
— Scleroderma and its causation. 304
— (Collip and Thomson): Effect of hypophysectomy upon pregnancy and lactation in mice 749
— — Nervous and hormonal factors in lactation 237
— cf. Collip 639
— cf. Pugsley 762
Severinghaus, A. E.: A cytological study of the anterior pituitary of the rat, with special reference to the Golgi apparatus and to cell relationship 755
Sevringhaus, E. L.: The use of folliculin in involutional states. 749
Sexton, D. L.: Treatment of sexual development in human male with anterior pituitary-like hormone of urine of pregnancy... 47
Shcherbakov, S. A. (Zimnitskii, Vishnevskii and Zatornitzkaya): Action of pain stimuli on internal secretions of adrenals, pancreas and blood sugar 302

Shelesnyak, M. C.: The production of deciduomata in immature rats by pregnancy urine treatment 430
— The production of deciduomata in spayed immature rats after oestrin and progestin treatment 430, 550
Sherman, I.: cf. Goldzieher 505
Sherman, J. E.: cf. Morris.....282
Sherwood, T. C. (Savage and Hall): The effect of amniotin on the basal metabolism of rats and rabbits 431
— (Toth and Carr): Effects of cod-liver oil on basal metabolism and on the thyroid gland 254
Shinobe, S.: Studies on influence of various glands of internal secretions on gas exchange in animals suffering from B avitaminoses. II. The influence of insulin 302
Shirer, J. M.: Hypermotility of the gastro-intestinal tract in hyperthyroidism; a study of 42 cases.316
Shoemaker, Rosemary: cf. Murphy 203
Shumacker, H. B. (Firor): Interrelationship of adrenal cortex and anterior lobe of hypophysis 676
Siehrs, A. E. (Miller): Disappearance of vitamin C from adrenals of guinea pigs having scurvy 147
Simpson, Miriam E.: cf. Evans... .....601, 607
Simpson, S. L.: cf. Bernhardt...543
Sitsen, A. E.: Normal organ weights 284
Sjollema, B.: cf. Seekles.....290
Skipp, W. M.: Pituitary headache.596
Sloan, L. W.: cf. Gutman.....451
Smelser, G. K.: cf. Nelson.....289
Smith, A. M.: Roentgen therapy of exophthalmic goiter 591
Smith, G. C.: cf. Riddle.....283
Smith, G. V. S. (Rock): Dysfunctional uterine bleeding, results in treatment with extracts of the urine of pregnant women..431
Smith, P. E.: Increased skeletal effects in anterior pituitary growth-hormone injections by administration of thyroid in hypophysectomized, thyroparathyroidectomized rats.....441
— (Leonard): Effect of injecting pregnancy-urine extracts in hypophysectomized rats; the male. Effect of injecting pregnancy-urine extracts in hypophysectomized rats; the female. Mating reaction of hypophysectomized male rats treated with pregnancy-urine extracts 441
Soeken, G.: On the physiology of puberty; the excretion of anterior pituitary hormone-A in urine 755
Solá, E.: Malignant goiters.....316
Solari, L. A.: cf. Artundo.....750
Solomon, E.: cf. Labbé.....312
Soskin, S.: cf. Strouse.....446
Spence, A. W.: Basal oxygen consumption of goitrous and non-goitrous rats 316
Spielman, F. (Goldberger and Frank): Hormone diagnosis of viability of pregnancy.....431
Stanley, L. L. (Hawkins): Implantations of anterior pituitary glands in alopecia 441
Starr, P. (Patton): Effect of pregnancy urine extract and ovarian follicular hormone on hyperthyroidism 113
Stein, S. I.: Experimental studies on the hypophysis cerebri. III. Effect of several pregnancies in the albino rat.....721
— The effect of castration on the hypophysis cerebri of the male albino rat 156
Steinach, E. (Kun): Lutein tissue and male sex characters 290
Steinberg, D. L.: cf. Nerancy....642
Stella, G.: The action of adrenaline upon the cardiac vagus centers 279
Stockheim, W.: The mode of action of thyroxine 765
Stoll, H. F.: Chronic invalidism with marked personality changes due to myxedema.....453
Strouse, S. (Soskin): Treatment of the same diabetic patient with widely varying diets.....446
tum Suden, Caroline: cf. Wyman.147
Sullivan, E. A.: Insulin therapy in post-pellagrous trophic ulcers 760
Sullivan, Ruth C.: cf. Zwemer.97, 730
Svirbely, J. L. (Szent-Györgyi): Function of adrenal medulla...279
— cf. Annau 739
Swezy, Olive: Hormones of hypophysis of infantile rat.....619
Sykes, J. F.: cf. Taylor.....447
Szent-Györgyi, A.: Hexuronic acid as antiscorbutic factor.....279
— cf. Annau.....739
— cf. Svirbely 279

Tainter, F. J.: Case of homo transplant of parathyroid for tetany.304
de Takats, G. (Cuthbert): Surgical attempts at increasing sugar tolerance 760
— (Fenn): Bilateral splanchnic nerve section in a juvenile diabetic 653
Talbot, F. B.: Interpretation of basal metabolism in children...637

Tanino, F.: The iodine and bromine content of the thyroid....663
Targow, A. M.: Effect of growth-promoting extracts of bovine anterior hypophysis on hypophyses of castrated albino rats...441
Taubenhaus, M.: A case of calcification of the pineal gland associated with other endocrine disturbances 304
Taylor, F. B.: cf. Lisser.....333
Taylor, J. M. (Wolfermann and Krock): Arrhenoblastoma of the ovary 431
Taylor, N. B. (Weld and Sykes): Vagal innervation and parathormone 447
Taylor, S. G.: cf. Thompson.....228
Tchernozatonskaia, E. P.: Use of pregnancy urine and prolan in animal industry 482
Tedstrom, M. K.: Hypoglycemia and hyperinsulinism 760
Thannhauser, S. J. (Fuld): Insulin-refractory diabetes mellitus.446
Thomas, Gertrude: cf. Greisheimer 444
Thomas, W. A.: Generalized edema occurring only at the menstrual period 647
Thompson, J. H.: cf. Robinson...303
Thompson, Juanita: The effect of rachitogenic diets on the thyroid gland of the albino rat...316
Thompson, Phebe K.: cf. Thompson 228, 664, 665
Thompson, W. O. (Thompson and Dickie): Monosodium thyroxine, desiccated thyroid and an impure sodium salt of thyroxine; comparison of their effects when administered orally with the effect of thyroxine injected intravenously in alkaline solution 664
— (Thompson, Dickie and Alper): Effect of alkali on the absorption of thyroxine from the gastro-intestinal tract; with a note on the comparative effects of synthetic and "natural" thyroxine injected intravenously 665
— (Thompson, Alper and Dickie): Effect of various compounds of thyroxine on basal metabolism 228
Thompson, W. H. (Ziegler and McQuarrie): Effects of pituitary antidiuresis on non-cardiac edema 156
Thomson, D. L. (Pugsley): On the mechanism of parathyroid hormone action 304
— cf. Collip 71, 639
— cf. Selye 237, 749
Tihomirov, D. M.: cf. Pavlovic..657
Topper, A.: Standards of basal metabolism for children of retarded growth 638
— cf. Schick 637
— (Mulier): Basal metabolism in asthma and epilepsy 665
— cf. Schwarz 665
Torigoe, M.: cf. Tweedy.....657
Torres, Isabel: cf. Collazo.....739
Toth, L. A.: cf. Sherwood.....254
Trautwein, H.: cf. Oefelein.....545
Trinquier, E.: cf. Aubertin..648, 649
Tsai, C.: cf. Lin.....288
Tschaikowsky, W. K.: Physiologic action of folliculin upon the pregnant 432
Tschumi, H.: cf. Asher 306
Turcatti, E.: cf. Lewis.....652
Turner, C. W.: cf. Gardner.....436
Tweedy, W. R. (Torigoe): Chemical studies on a parathyroid hormone 657

Uebelhör, R.: cf. Mandel.....160
Ueno, A. (Murata): Hormone content of anterior lobe of human hypophysis 297
Ungar, I.: Cause of hyperkeratosis produced in toads by hypophysectomy and lesion of the tuber cinereum 441
Uotila, U.: cf. Räihä 663
Üprus, V.: Experimental investigations on the transplantation of ovaries which have been kept at low temperatures 290

Van der Kaay, F. C.: cf. Seekles.290
Van Dyke, H. B.: cf. D'Amour..293
Vastola, A. P.: Embryonal carcinoma of abdominal testis in a pseudohermaphrodite 152
Verzár, F. (v. Arvay and v. Kokas): Basal metabolism associated with E avitaminosis and the relation of anterior pituitary hormone 297
Viale, G.: Adrenalinemia and adrenalinuria 426
Vick, R. M.: cf. Elmslie 160
Vidacovitch, M.: cf. Hermann...741
Vidal, J.: The influence of partial and total adrenalectomy on the results of diabetic piqûre of the bulb 742
Vinâls, E.: Influence of the follicular hormone on the plumage of the pigeon and of Vanellus chilensis 291
Vishnevski, A. A.: cf. Shcherbakov 302
Visscher, M. B.: cf. Peter.....303

Wadehan, F.: cf. Glimm.....288
van Wagenan, G.: Uterine bleeding of monkeys in relation to neural and vascular processes; spinal transection and menstruation 151
Walawski, J.: Influence of adrenine on the blood pressure curve in asphyxia.....280
Wan, S.: cf. Lin.....288
Ware, H. H., Jr. (Main): Observations on the accuracy of the rabbit ovulation test for pregnancy 432
Watrin, M. (Brabant): Hysterectomy and the structure of the ovary 291
Watson, E. M.: The association of diabetes mellitus and pernicious anaemia 653
Wechsler, H. F.: cf. Packard....146
Weichert, C. K. (Boyd): Induction of typical pseudopregnancy in the albino rat by means of experimental hyperthyroidism .766
Weigel, W.: cf. Ehrhardt.....745
Weisenburg, T. H.: Tumors in the pituitary area, the neurologic symptoms 297
Weinstein, A.: cf. Harrop.....544
Weinstein, M. L.: Acute suppurative thyroiditis with report of one case 454
Weld, C. B.: cf. Taylor.....447
Weller, C. V.: Hepatic pathology in exophthalmic goiter.....665
Welton, Arthur D.: cf. Mayer...423
Werner, A. A. (Collier): Production of endometrial growth in castrated women; minimum dosage of theelin that is required..749
——The effect of theelin injections on the castrated woman 291
White, Priscilla: cf. Pincus.....159
White, P.: cf. Joslin.....444
White, W. E.: The effect of hypophysectomy on the survival of spermatozoa in the male rat...298
— (Leonard): Ovarian responses to prolan and anterior pituitary extract in hypophysectomized rabbits with particular reference to ovulation...298
Whitehead, R.: Cortical proliferation in the mouse suprarenal after peptone 426
— Significance of natural variations in structure and cortical lipoid of mouse suprarenal 280
Widenhorn, H.: cf. Harrop.....544
Widmann, E.: Schneider 664
Wiedner, E.: Abelin 548
Wiesner, B. P.: The experimental study of senescence 151
Wilder, R. M. (Foster and Pemberton): Total thyroidectomy in diabetes mellitus 455
Wilkinson, S. A.: Gastric acidity in thyroid dysfunction 766
Williams, J. L. (Dick): Decreased dextrose tolerance in acute infectious diseases 653
Wirz, P.: Anterior lobe pituitary hormone and amenorrhea 299
Wislánski, K.: Internal secretion of pineal gland and the therapeutic use of its extracts.....304
Wislocki, G. B.: Observations on the descent of the testes in the macaque and in the chimpanzee.643
Witherspoon, J. T.: Cause of onset of labor; an hormonal investigation 432
— The interrelationship between ovarian follicle cysts, hyperplasia of the endometrium, and fibromyomata; a possible etiology of uterine fibroids..432
— The treatment of menstrual disorders by the injection of blood from pregnant donors.550
Wolfe, J. M. (Cleveland): Cyclic histological variations in the anterior hypophysis of the albino rat 157
——Pregnancy changes in the anterior hypophysis of the albino rat 647
— cf. Cleveland 644
— cf. Ellison 555
Wolfermann, S. J.: cf. Taylor...431
Womack, N. A.: cf. Cole.....307
Wright, D. O.: cf. Musser.....445
Wurmser, L.: cf. Choay.....293
Wyeth, G. A.: Histological findings of hypophysis in cancer... 59
Wyman, L. C. (tum Suden): Studies on suprarenal insufficiency; the growth of transplanted cortical tissue in the rat.147

Yamada, S.: On the effect of insulin, epinephrine and phlorhizin on the lactic acid content and the distribution of phosphates in the blood of rabbits..284
Young, A. M.: Five hundred and nineteen Voge bromine tests of urine for pregnancy 749
Young, H. H.: Some hermaphrodites I have met.....750
Yriart, M. (Gotta): Glucose metabolism in hyperthyroidism...454

Zatornitzkaya, Z. A.: cf. Shcherbakov 302
Ziegler, Mildred: cf. Thompson..156
Zillessen, F. O.: cf. Kincov.....361
Zilva, S. S.: Hexuronic acid as the antiscorbutic factor 280

Zimmerman, O.: Blood constituents in Basedow's disease 454
Zimnitzkii, V. S.: cf. Shcherbakov.302
Zondek, B. (Krohn): Hormone of pars intermedia of the pituitary gland 299
— cf. Zondek 300
Zondek, H.: Chemical findings in psychiatric patients; relations to the hormonal system.....442
— (Koehler): The treatment of hypophyseal cerebral emaciation with hormone of the anterior lobe of the pituitary, Prolan 442
— (Zondek and Hartoch): Prolan and growth of tumors; inhibiting influence of prolan on growth of tumors in white mice 300
Zollinger, R. (Cutler): Aneurysm of the internal carotid artery; report of a case simulating tumor of the pituitary 648
Zuckerman, S.: The comparative physiology of the menstrual cycle 433
Zunz, E.: Studies on the influence of adrenine on the reduced glutathione in the blood.....636
— (La Barre): Action of thyroxine on the secretion of adrenaline 636
Zwarenstein, H.: cf. Schrive.....290
Zwemer, R. L.: Adrenal cortex and electrolyte metabolism ...161
— (Sullivan): Blood chemistry of adrenal insufficiency in cats. 97
— — Corticoadrenal influence on blood sugar mobilization.730

SUBJECTS

Acromegaly and blood sugar.....755
— onset of, before 15 years of age.643
— report of a case..... 20
Addison's disease, adrenal cortical therapy in 333
— — and adrenal cortical extract.256
— — — blood sugar 755
— — calcification of adrenals in..143
— — catalase studies in.....545
— — digestive symptoms in.....497
— — effects of an excess of cortical hormone in.....361
— — sodium salts in treatment of.161
— — treated with adrenal cortical extract 145, 277
— — treatment of 341
— — — — — with cortin (Hartman) 275
— — with atrophy of adrenal cortex 740
Adrenal ablation and basal metabolic rate of rabbit 311
— — — circulation 634
— — — diabetes 742
— — — experimental cancer 742
— — — fat content of various organs 277
— — — hypoglycemic ability of insulin 445
— — — lactic acid formation during muscular work ...275
— — — temperature studies 544
— — — traumatic shock 276
— — — tumor growth 742
— — — — tissue grafts.....743
— — catalase studies in.....545
— — effects of 275
— — studies on 545
— — temperature studies after..278
— and cirrhosis of liver.....280
— — gonad-stimulating principle of anterior lobe of pituitary 123
— — hypophysis sex hormone...426
— — insanitary conditions 453
— — metabolism 179
— — muscle metabolism 543
— — oestrous cycle 143
— — pain stimuli 302
— — splenectomy 277
— — temperature regulation 276
— — thymus antagonism 305
— — vitamin C 147
— calcification of, in Addison's disease 143
— chemistry of 278
— cortex and blood disorders....636
— — — electrolyte metabolism ..161
— — — hypophysis ablation 649
— — — sexual development.....741
— — atrophy in Addison's disease.740
— — certain functions of.....740
— — extracts and blood cholesterol 739
— — — — oestrous cycle 144
— — — — reproductive system..145
— — — further studies on 145
— — — in Addison's disease....277
Adrenal cortex extracts in hyposuprarenalism 279
— — — — — treatment of bronchial asthma.....425
— — — — reaction to, in schizophrenic and normal subjects 576
— — hormone and hypophysis...550
— — — — metabolism 544
— — — — — myasthenia gravis ...543
— — — — further observations on.276
— — influence of, on blood sugar.730
— — insufficiency and hyperemesis gravidarium 544
— — internal secretion of 741
— — preparation of an active extract of 634
— — relation of, to anterior lobe of hypophysis 676
— cortical extract and asthenia..437
— — — — — oestrus cycle 145
— — — — — sex function 144
— — — — biologic estimation of...276
— — — — effects of, on blood.....633
— — — — in Addison's disease....145
— — hormone and blood cholesterol 393
— — — — — tissue respiration ...544
— — — — effect of excess of in Addison's disease 361
— — — — in urine 634
— — therapy in Addison's disease.333
— — tissue transplants, growth of 147
— denervation and sugar tolerance 760
— disorders in the Southeast....221
— effect of gonad ablation on....744
— — — — male sex hormone...429
— extract, action of, on cardiac vagus centers 279
— — — — — thyroxine on.....636
— — and albumin-globulin ratio.147
— — — — anesthetics 281
— — — — blood cholesterol 143
— — — — — pressure in asphyxia.280
— — — — — sugar 301, 650
— — — — hyperglycemia 645
— — — — insulin antagonism 301
— — — — — in, relation between..301
— — — — lymph node extract 281
— — — — nitrogen excretion 651
— — — — phosporous poisoning...278
— — — — secretion of sweat 633
— — — — sodium chloride content of bile 283
— — — — sperm motility 546
— — — — sugar tolerance 651
— — effect of injections of from mother to foetus 638
— — — — — on blood pressure after ergotoxine 146
— — — — — — eye reactions after pancreas ablation 652
— — — — — — free muscle sugar and total carbohydrate 635

Adrenal extract, effect of on lactic acid and phosphates in blood..284
——— epinephrine, and anaphylactic shock 144
——— hyperglycemia and hypophysis 295
——— in body fluids 633
——— treatment of whooping cough 739
——— influence of on anterior lobe of hypophysis.....752
——— injections and pulmonary oedema 635
——— tumor-inhibiting properties of 633
———-genital syndrome 279
— gland, a suprarenalin-producing pheochromocytoma of 634
——— carotene of 739
——— denervation and experimental diabetes 740
——— extract in Addison's disease.341
——— hypertrophy and hypophysis extracts 740
——— in health and disease.256, 361
— hemorrhage and death in epilepsy 425
— in muscle glycogen recovery...739
— influence of on genital function 423
——— metamorphosis 276
— insufficiency and blood chemistry 97
——— malnutrition 146
——— pancreatic diabetes 652
——— digestive symptoms in.....497
——— experiments in animals....146
— medulla and respiratory metabolism of diabetes.....159
——— function of 279, 739
——— sympathetic tumors of.....546
— mitoses in, after peptone.....426
— quantitative studies on cortex and medulla of 277
— secretion, effect of dehydration on 425
— significance of natural variations in structure and cortical lipoid of 280
— specificity of hypoglycemia hormone of 279
— stimulation of ovary 249
— use of cortin following removal of tumor of.....425
— weight changes and diet.....367
——— of 284
Adrenaline discharge and compression of eyeball 741
— pressure of in blood and urine.426
Advanced ossification in children.117
Amenorrhea and anterior lobe hormone 299
——— x-ray irradiation 148
— hypophysis and ovary hormone in 149
— treatment of with combined female sex hormones 430
Amniotin, effect of, on basal metabolism 431
Anterior pituitary-like fraction of pregnancy urine and testicular descent 475
——— hormone and uterine bleeding 551
Aschheim-Zondek pregnancy test on adult ovary 437
Authors, numerous: Constitution and constitutional anomalies ..147
— several: Genetics, especially human 147

Basal metabolic rate and suspension stability of blood 765
——— determination as guide to therapy 764
——— in acromegaly 20
——— in endemic cretins 451
——— standards and growth retardation 638
— metabolism and advanced ossification 117
——— anterior lobe extract.... .....658, 750
——— pituitary hormone ...297
——— extract of urine of human beings with toxic goiter 307
——— slow pulse rate 637
——— effect of amniotin on.....431
——— anterior lobe extract on 752
——— pituitary extract on.152
——— cod-liver oil on.....254
——— thyroxine on 228
——— in asthma and epilepsy....665
——— children, interpretation of 637
——— relation of, to body build 637
——— mothers, relation of, to infant birth weight...453
——— influence of hypophysis on.409
——— relation of hypophysis and thyroid to 660
— oxygen consumption of goitrous and non-goitrous rats.....316
Basedow's disease, blood constituents in 454
——— iodine-x-ray treatment of..308
——— mitogenetic rays of blood in.315
Blood calcium, action of gonadotropic hormone on 654
— chemistry and adrenal insufficiency 97
——— effect of Ringer's solution on, after thyroparathyroid ablation 654
— chloride, effect of adrenal cortex extract on 161
— cholesterol and adrenal cortex extracts 739
——— cortical hormone 393
——— extract 143
——— effect of pregnancy urine of.641
——— in myxedema 665
——— thyroid disease 660
— constituents, effect of adrenal cortical extracts on 633
— disorders, influence of endocrine system in 636

Blood flow, effect of thyroid feeding on 310
— glutathione and hypophysis ... 753
— iodine, action of extracts of anterior lobe of hypophysis on. 437
— — and anterior lobe extract ... 295
— lipids and anterior pituitary lobe extract 439
— pressure and depression substance in pancreas 462
— — — ergotoxine 146
— — — hypophysis 292
— — — obesity 445
— sodium, effect of adrenal cortex extract on 161
— studies in case of acromegaly. 20
— sugar after hypophysis ablation 552
— — and anterior lobe extract of hypophysis 437
— — — hypophysis ablation 644
— — — insulin 650
— — — — reaction 759
— — — low carbohydrate diet ... 444
— — — pain stimuli 302
— — — posterior pituitary extract 554
— — changes during delivery 759
— — corticoadrenal influence on. 730
— — curve and infection; in children 75
— — effect of adrenal extract and insulin on 301
— — — — insulin on, during infection 157
— — influence of anterior lobe of. 291
— — — — hormones of 650
— — values in clinical diagnosis. 755
Bromide, effect of, on thyroid ... 170

Calcium, effect of, on thyroid 170
— metabolism, action of parathyroid hormone on 762
— rich diet and experimental colloid goiter 197
— salts and heart efficiency 303
Calorigenic action of thyroid 317
Cancer and hypophysis, relation of 59
Carbohydrate and adrenal extract. 635
— metabolism and hypophysis extract 434, 554
— — control of 445
— — in acromegaly 20
— — — hyperthyroidism 454
— — — hypophysis ablation 153
Carotid artery, aneurysm of, simulating tumor of hypophysis ... 648
— sinus and insulin sensitiveness. 300
Castration and experimental cancer 742
— — growth-promoting hormone of hypophysis 441
— — hypophysis extract 429
— — sperm survival after hypophysectomy 297
— — theelin injections 291
— — tumor growth 742
— — — tissue grafts 743
— effect of, on adult weight 286
— — — — hypophysis 156, 555
Castration production of endometrial growth by theelin after ... 749
Chloride, effect of, on thyroid 170
Cholecystokinin, effect of, on grafted gall bladder 282
Comb-growth promoting substance in male urine 150
Constitutional anomalies 147
Corpora lutea formation and anterior lobe extracts 752
Corpus luteum and anterior lobe hormone 296
— — — extracts of pregnancy urine 287
— — — lactation 289
— — — post pituitary hormone .. 432
— — extract and pregnancy 745
— — — — uterine motility 289
— — — influence of on anterior lobe of hypophysis ... 752
— — hormones 667
— — and ovarian hemorrhage ... 748
— — — investigation of 745
— — influence of, on maternal instinct 745
— — physiology of 423
— — relation between gravid uterus, and, in late pregnancy 747
Creatine metabolism and ovary ... 430
— — influence of sex hormones on 427
Cryptorchidism in guinea pigs 638, 747
— and pituitary-testis-prostate relationship 123
— — pregnancy urine hormone .. 47
Cushing's syndrome, case of 152

Dextrose tolerance in acute infectious diseases 653
Diabetes and adrenal ablation ... 742
— — blood sugar 755
— — hypophysis 159
— — — ablation 554
— — infection in children 75
— — pernicious anemia 445
— — pregnancy 649
— bilateral splanchnic nerve section in 653
— choline and liver fat in 756
— effect of glucose and insulin in. 302
— epilepsy and convulsions in ... 651
— experimental, and adrenal gland denervation 740
— fat control in 758
— hypoglycemic symptoms in 652
— in children and diet 651
— influence of hypophysis on 553
— insipidus and abnormal mental states, encephalography in .. 647
— — in case of xanthomatosis ... 152
— — use of pituitrin in 754
— lactation in 757
— mellitus, a case of brain tumor simulating 652
— — analogy between adrenal insufficiency and 341
— — and arteriosclerosis 759
— — — parotid hypertrophy ... 443

Diabetes mellitus and pernicious anaemia 653
———— pineal calcification 304
———— retinal pathology 757
———— total thyroid ablation...455
—— latent tolerance in 300
—— on the inheritance of.....159
—— refractory to insulin 446
—— staphylococcic infections in.650
—— symptomatology of 759
— pancreatic, eye reactions in...652
— treatment of 442
———— with widely varying diets 446
Diabetic coma 444
—— uncontrollable causes of death in 158
— effects of anterior lobe hormone 553
— syndrome and anterior lobe extract 435
Diet and adrenal weight.....367
Digestive symptoms in Addison's disease 497

Emmenin, chemical nature of.... 71
Endocrine diseases, visual fields in.282
— disturbances and secretion of anterior lobe hormone in urine 552
— dwarfism, treatment of 387
— dystrophies, sero-interferometer method for determining.281
— factors in sex 423
— functions in senility 151
— glands and nervous disease...426
———— post-infectious metabolism 637
—— in bodily adjustment 142
—— influence of on development and maintenance of experimental cancer 742
—— test for activity of 742
— influence on male sex organs..429
— observations on advanced ossification 117
— statistics from the Southeast..221
Endocrinology of sex, periodicals on 421
Endocrinopathy and the psychoses.283
Epilepsy and convulsions in diabetes 651
Estrin, new procedure for demonstration of 705
Estrous, relation of anterior lobe sex hormone to 751
Estrus and hypophysis 293
— effect of anterior lobe extracts of hypophysis on.....434
— producing extract in blood of normal women 286
—— hormone, international standard for 149
Exophthalmic goiter and fluoride treatment 309
———— pathologic anatomy of the liver 763
———— progressive muscular atrophy 701
———— vegetative nervous system 312
Exophthalmic goiter, cardiovascular symptomatology in.....661
—— clinical and experimental studies of 664
—— hepatic pathology in.....665
—— roentgen therapy of.....691
—— spontaneous glycosuria in..447
— and sporadic goiters 306

Fat metabolism and adrenal function 179
— tolerance test in pituitary disease 505
Female reproductive system and hypophysis 601
— sex hormone and testis.....150
———— clinical trials with.....430
———— comparative studies of..548
———— in treatment of mastodynia 287
———— urine 288
Fertility and follicular hormone..640
Fluoride, effect of, on thyroid...170
Follicular hormone, action of....640
— stimulating factor of hypophysis 435

Gaseous metabolism and gonadotropic principle of pregnancy urine 642
Gland extirpation and tumor tissue grafts 743
Glucose tolerance, effect of carbohydrate and fat diets on....444
Glycemia, modifications of.....756
— in exophthalmic goiter.....447
Goiter and basal oxygen consumption 316
— racial incidence and relation to nutrition 658
— relation of, to chronic foci infection 658
Gonad ablation, effect of, on adrenal, thyroid and pituitary 744
— and adrenal cortex extract....145
———— relation between 341
—— cirrhosis of liver 280
—— pineal extracts 304
— disorders in the Southeast....221
— effect of certain drugs on.....235
———— x-ray on 123
— influence of, on protein metabolism 290
— male, effects of pituitary implants on 86
— of fetal horses, hormone content of 548
— relation of, to adrenals 249
—— to anterior lobe of hypophysis 751
— seasonal variation in size of..283
— stimulating hormone and ovulation 286
———— comparative studies of 428, 746
—— of hypophysis and thyroid hypertrophy 156
———————— hypophysis, effect of on immature female rats 438

Gonad stimulating power of hypophysis after adrenal ablation..676
——————— effect of prolan on.640
—— principle of mare serum...285
Gonadotrophic extracts, production of ovulation by 714
— function of anterior lobe of hypophysis 751
— hormone, action of, on tetany and blood calcium 654
—— and vitamin A 743
—— of hypophysis 292
—— in urine of case of teratoma testis 629
— principle of pregnancy urine and gaseous metabolism ...642
— substances in urine of pregnancy 1
Graves disease and liver involvement 665
—— extracts of anterior lobe of hypophysis in 434
—— non-surgical treatment of..449
—— psychogenic factors in.....313
Growth and adrenal cortex.....740
—— parathyroid ablation.....655
—— thymus extract 657
— effect of pregnancy urine and prolan on 482
— experiments on effect of injection of extracts from aged and embryonic animals 637
— hormone of hypophysis, effect of, on body and tail lengths.754
— retardation and basal metabolism 638

Headache, pituitary treatment of.596
Hemochromatosis, case of.....742
Hepatic pathology in exophthalmic goiter 665
Hermaphroditism, case of.....750
Hexuronic acid as antiscorbutic factor 279, 280
Hirsutism and virility, pathology of 429
Hormonal sterilization of female organism 639
Hormone concentration in skin during pregnancy 429
— diagnosis of viability of pregnancy 431
— factors in lactation 237
— in cancer 742, 743
— of hypophysis of infantile rat.619
— passage from mother to foetus.638
— responses and drugs.....235
Human genetics 147
Hyperglycemia, action of anterior lobe extract on 645
— and anterior pituitary lobe transplants 433
—— respiratory quotient 158
— constituents in normal urine producing 382
Hyperinsulinism, a definite disease entity 758
— and hypoglycemia 760
— cured by surgical intervention.649
Hyperparathyroidism and rickets.654
— effect of phosphate ingestion in.302
Hyperthyroidism and adrenal cortical extract 256
—— blood sugar 755
—— diabetes 75
—— fluoride treatment 309
—— hypermotility of gastro-intestinal tract 316
—— iron excretion 306
—— pseudopregnancy 766
—— vitamin B 307
— cardiac manifestations of.....447
— diagnosis and treatment of....315
— effect of diiodotyrosine in.....451
———— ovarian follicular hormone of 113
———— pregnancy urine extract on 113
— heart in 307, 311
— induction of pseudopregnancy by experimental 766
— iodine tolerance test for.....487
Hypoglycemia and hyperinsulinism 760
— mechanism of 759
— neurological manifestations of.758
Hypoglycemic action of insulin...648
— effect of insulin injected into portal system 648
Hypogonadism in male, diagnosis of 289
Hypophyseal cachexia 553
Hypophysis ablation and adrenal cortex hormone 550
———— asthenia 437
———— blood sugar 644
———— diabetes 159, 554
———— effect of anterior lobe extract on metabolism..752
———— follicular atresia in ovaries 293
———— hyperkeratosis 441
———— nitrogen metabolism ...292
———— ovary changes 153
———— phosphocreatine and glutathione in muscle ...646
———— skeletal growth 441
———— specific dynamic action..439
———— thyroid feeding in snakes.453
—— effect of, on pregnancy and lactation 749
—— in pregnant rat 646
—— transmission of polyuria and hypochloruria following..644
— action of alkaline extracts of anterior lobe on immature guinea pigs 644
———— anterior lobe extracts of, on blood iodine 437
———————————— thyroid weight and histology .645
———————— hormone of on ovary 752
———————— extract in headache.295
———————— of, on kidney..554
———————— injected into cervix uteri 294
———— sex hormone of, on testes.753
— and adrenal cortex relationship.676
—— advanced ossification 117
—— basal metabolism 297

Hypophysis and blood glutathione. 753
——— pressure 292
——— sugar 291
—— cirrhosis of liver..... 280
—— compensatory hypertrophy of thyroid 660
—— diabetes insipidus in batrachians and reptiles 553
—— eclampsia 312
—— estrus 293
—— female reproductive system. 601
—— generalized edema during menstruation 647
—— headaches 551
—— hyperglycemia 75, 433
—— hypothalamus, anatomical connections between 647
—— lactation 237, 289
—— lipoid metabolism 152
—— male reproductive system.. 607
—— metabolism 295
—— muscle glycogen 552
—— nitrogen metabolism in toads 643
—— ovary 148
——— interrelationship between. 149
—— ovulation 206
—— pancreas relationship of... 649
—— placenta extracts, action of. 294
—— pregnancy urine extracts... 441
—— reproduction 288
—— reproductive glands 282
——— system 423
—— senescence 151
—— sperm survival 297
—— thyroid ..... .662, 291, 295, 310, 315, 438
——— activity 434
——— in relation to basal metabolism 660
——— relation of, to molting.. 743
——— relationship 434
—— tuber cinereum indirect endocrine relationship between 754
—— uterine implants of carcinoma 436
— anterior and posterior extracts of, and intestinal permeability 154
—— lobe and castration 751
——— extract and blood iodine. 295
——— iodine content in blood and thyroid 293
——— insulin 432
——— lactation 435
——— melanophore reaction 644
——— nitrogen metabolism 153
——— ovulation 298
——— sex activity 296
——— thyroid 551
——— weight 294
——— of, and basal metabolism 152
——— blood glutathione 439
——— lipoids 439
——— sugar 437

Hypophysis, anterior lobe extract of and estrus..... 434
——— hyperglycemia .645
——— lactation 33
——— luteinization ..752
——— phlorizin diabetes 438
——— plasma proteins. 436
——— in Graves' disease. 434
——— case of Laurence-Moon-Biedl syndrome ...583
——— hormone and amenorrhea 299
——— corpus luteum ...296
——— tumor growth 191
——— in urine 554
——— and endocrine disturbances 552
——— and mammary gland development 153
——— in urine 755
—— pituitary hormone of, in blood during pregnancy.. 553
—— sex hormone of and estrous. 751
— antidiuretic potency of posterior lobe extract of 292
— biological evaluation of colloid of beef 296
— bromine in anterior lobe of... 442
— carbohydrate metabolism in partial ablation of..... 153
— case of basephil adenoma of anterior lobe of..... 152
— cyclic histological variations in. 157
——— anterior lobe of. 644
— cytological study of anterior lobe of 755
— diabetic effect of anterior lobe extract of 553
— diabetogenic principle of anterior lobe of 435
— differentiation of functions of anterior lobe of..... 440
— diseases of 754
— disorders in the Southeast.... 221
— effect of anterior lobe extract of, after thyroid ablation... 752
——— on basal metabolism .750
——— conception and pregnancy .428
——— growth of mice ..439
——— seminal vesicles 287
——— thyroid ..658
——— blood disorders 636
——— antidiuretic extract of on edema 156
——— castration on..... 156, 555
——— different extracts of anterior lobe of, on sex organs 641
——— gonad ablation on 744
——— gonad-stimulating hormone of, on immature female rats 438
——— principle of 123

Hypophysis, effect of growth hormone of, after castration 441
——————— on body and tail lengths 754
——————————— growth, ash nitrogen and energy balance ..154
———— luteinizing and follicular stimulating fractions of, on thyroid 436
———— prolan on potency of....640
———— several pregnancies on..721
———— thyroid feeding on anterior lobe of.....766
— extracts and adrenal gland hypertrophy 740
———— albumin-globulin ratio..147
———— anesthetics 281
———— insulin hypoglycemia ...554
———— luteinization of ovary...513
———— maturity 750
———— ovary weight 428
———— ovulation 539
———— sperm motility 546
———— sugar tolerance.....651
———— thyroid 451
—— effect of, on prostate.....429
—— in treatment of infantilism.233
—— of anterior lobe of and insulin resistance 643
——————————— susceptibility to lack of oxygen ...660
— fat tolerance test in diseases of 505
— further purification of follicular-stimulating factor of....435
— gonadotropic hormone of.....292
———— and ovulation 714
——————— prolan 755
— gonad-stimulating hormone and thyroid 156
— growth hormone and dwarfism.387
———— thyroid extract in skeletal growth 441
———— liver and kidney metabolism 440
— gumma of 751
— histological origin of hormones of posterior lobe of.....750
— hormones and male gonads...440
———— ovary 290
—— content of anterior lobe of.296
—— in blood and urine of pregnancy 295
—— of anterior lobe of.....435
———— infantile rat 619
———— pars intermedia of.....299
———— posterior lobe of, and pregnancy toxicoses ..746
—— prolactin 155
—— use of, in amenorrhea.....149
— hyperglycemia and alcohol....554
— implantation of anterior lobe of, in alopecia 441
— influence of hormonal substances on function of anterior lobe of 752
Hypophysis, influence of hormone of anterior lobe of, on metabolism of testes 440
———— on basal metabolism and specific dynamic action.409
— insufficiency and familial infantilism 533
— lactation-stimulating hormone of 436
— melanophore hormone content of posterior lobe of.....434
— mouse unit of anterior pituitary, hormone B of.....553
— neurological symptoms of tumors of 297
— oxytocic factor of posterior lobe of, and cerebrospinal fluid..294
—— properties of powdered posterior lobe of 293
— parathyreotropic action of extracts of anterior lobe of....350
— pathology of 274
— percentage of different types of cells in anterior lobe in adult human female 754
— posterior and anterior lobe extracts of, in headache 596
—— lobe extract and imbibition in Batracians 646
——————— weight changes ...644
———————— of and water metabolism 439
——————— use of, in labor.....211
— pregnancy changes in anterior lobe of 647
— preparation of thyreotropic extracts of anterior lobe of...645
— reaction of ovaries to anterior lobe extract of 639
— relation of active principle of placenta, pregnancy blood and urine to.....639
———— anterior lobe of, to thyroid 552
———— to cancer 59
— rôle of, in adrenaline and morphin hyperglycemia 295
— secretions of, and control of melanophores 753
— section of stalk of, and pseudopregnancy 647
— sex hormone, action of, on endocrine glands 426
———— effect of, on immature ovary 429
—— specific differences in behavior of anterior lobe of.296
— silver staining in study of.....646
— specific sex difference in anterior lobe of 645
— thyroid-stimulating hormone of anterior lobe of 645
— treatment and thyroid 415
— use of anterior lobe extract of, in unexplained emaciation..442
— use of posterior lobe extracts of, in obstetrics 750
Hypopituitary obesity and high protein diet 154
Hypothalamus and hypophysis, anatomical connections between..647

Hypothalmus, experimental lesions of and blood sugar.....644
— gumma of 751
Hypothyroidism and heart disease.693
— iodine tolerance test for.....487

Infantilism, familial, due to hypophysis and thyroid insufficiency 533
— treatment of 233
Insulin absorption from gastrointestinal tract 443
— action and anterior lobe extract.432
— activation of 157
— administration to normal and diabetic persons, gastric secretion after 652
— and adrenal ablation 445
— — adrenaline antagonism 301
— — — relation between 301
— — albumin-globulin ratio 147
— — blood sugar 301, 650
— — dextrose tolerance in acute infectious diseases 653
— — diabetic coma 158
— — glucose in diabetes 302
— — hypophysis extract 554
— — liver fat 301
— — nitrogen excretion 651
— — protein equilibrium of the blood serum 652
— — respiratory quotient 158
— — sensitization of skin to x-rays 650
— — sodium chloride content of bile 283
— — sperm motility 546
— — sugar tolerance 651
— — — — in thin people 756
— — thermoregulation 443
— — vitamin B 302
— effect of, on blood pressure and pulse rate 756
— — — — — — sugar during infection 157
— — — — — hormone content of thyroid 314
— — — — — lactic acid and phosphates in blood ...284
— — — — — thyroid 663
— — — — thyroid extract on output of 636
— hypoglycemic action of 648
— in treatment of tuberculosis..648
— injected into portal system, effect of 649
— injections, comparison of effects of intravenous and subcutaneous methods of 648
— neuritis, case report of.....443
— protection of by antiproteases.157
— reaction and blood sugar.....759
— resistance and allergy.....157
— — — — anterior lobe extract....643
— — — — sensitivity 652
— secretion after radiation of pancreas region 759
— sensitiveness and carotid sinus.300
— therapy in nutrition disorders.444
— — — — post-pellagrous trophic ulcers 760
Insulin therapy in uterine bleeding.148
— treatment of menorrhagia 442
— use of in pulmonary tuberculosis 300, 650
Internal secretions, hereditary factors in 742
— — sociology of 423
Interrenal and chromaffine system of man 277
Intestine, hormone of, and hemoglobin in circulating blood.....188
Iodide, effect of, on thyroid.....170
— content of bile and urine after dried thyroid feeding.....763
— — — — human blood, significance of 658
— — — — thyroid 661, 663
— — — — — — and hypophysis extract 451
— deficient diet and experimental goiter 197
— diagnostic use of, in thyrotoxicosis 765
— insufficiency and stillbirths....661
— medication and metabolism in cretins 451
— metabolism and thyroid.....450
— presence of in tissues after thyroid feeding 762
— tolerance test for thyroid insufficiency 487
Islands of Langerhans, functioning tumor of 157
Islets of Langerhans, changes of, in pregnancy 649

Labor, cause of onset of.....432
Lactation and adrenal cortex.....740
— — anterior lobe extract 435
— — parathyroid ablation 655
— effect of hypophysis ablation on 749
— factors controlling 237
— — responsible for control of..436
— in diabetes 757
— physiology of 33, 289
Laurence-Moon-Biedl syndrome, case of 583
Liver damage and thyroid disease.664
— denervation and sugar tolerance 760
— effect of thyroid extract on...765
— extract in pernicious anemia..282
— pathologic anatomy of, and exophthalmic goiter 763

Male gonads, effect of hypophysis hormones on 440
— hormone, biochemical studies on 107
— — effect of, on seminal vesicles.287
— — in urine 289
— — injection of, in female guinea pig 428
— reproductive system and hypophysis 607
— sex characters and lutein tissue.290
— — organs, endocrine influence on 429

Male urine, comb-growth promoting substance in.....150
Males, adult, pituitary implants in 86
Malignant goiters 316
Mammary gland, clinical stimulation of 18
Masculinization and partial ovarian resection.....748
Maternal instinct, influence of corpus luteum on 745
Melanophores, humoral control of.547
Menopause and use of folliculin..749
Menstrual cycle, comparative physiology of 433
—— presence of follicular hormone in blood during ...705
— disorders, treatment of.....550
Menstruation and spinal transection 151
—— generalized edema 647
—— thyroid extract 211
— effect of pregnancy urine extract on 203
Mental disorders and ovary insufficiency 642
Metabolism and adrenal cortex...740
—— anterior lobe extract 153
—— hypophysis 295
— effect of adrenal cortex on....161
— in pregnancy 759
—— sex 423
Mongolianism in relation to age of mother 636
Mongolism, etiology of 636
— in monozygotic twins 637
Muscle glycogen restorage after vagotomy 757
— metabolism, relation of adrenal and thyroid to 543
Muscular atrophy and exophthalmic goiter 701
Myxedema and optic nerve neuritis 527
—— sporadic goiter 306
— effect of synthetic thyroxine in alkaline solution in.....665
——— thyroid extracts on.....664
— blood cholesterol in 665
— of childhood 662
— personality changes due to....453
— thyroid therapy in 317
—— treatment in 693

Nitrogen metabolism and pregnancy 428
—— effect of hypophysectomy on.643

Obesity and hypertension 445
Oestrin, chemistry of 149
Oestrous cycle and changes in adrenal 143
——— diet 288
——— protein intake 149
—— effect of adrenal cortical hormone on 145
— effect of adrenal cortex extract on 144
— stimulating power of powdered follicular liquid 639
Oestrin treatment and deciduomata production 430
Optic nerve neuritis and myxedema 527
Ovary ablation and fat distribution 150
——— lactation 33
— action of anterior lobe hormone on 752
——— follicular hormone of...640
— and action of drugs.....235
—— creatine metabolism 430
—— hypophysis ablation 153
——— interrelationship between.149
—— pancreas, relationship of...442
—— pineal extracts 304
—— thyroid 548
— arrhenoblastoma of 431
— changes and prolan B.....285
— effect of combined hypophysis sex hormone and pregnancy urine hormone 429
——— emmenin on 71
——— folliculin on development of 744
——— gonad-stimulating hormones on weight of...428
——— roentgen rays on.....547
— extract, absorption and elimination of, in man.....747
—— and abortion 745
——— deciduomata in spayed rats 550
——— endometrial growth after castration 749
——— genital development in new born 548
——— oestrus 747
——— ovulation 427
——— sperm motility 546
—— effect of, on adult ovary....744
—— influence of, on anterior lobe of hypophysis 752
—— response of feather follicle to 546
— follicular hormone and labor..432
— grafts in male guinea pigs.547, 640
— hemorrhage of, and corpus luteum hormone 748
— hormone and cervical trauma..549
——— changes in endometrium during menstrual cycle.284
——— milk secretion 155
——— pregnancy 432
—— in uterine bleeding.....148
—— influence of, on plumage color 291
—— of, and basal metabolism...431
—— test for efficiency of.....211
—— use of, in secondary amenorrhea 149
— influence of uterus on secretion of folliculin by 642
— inhibitory action of follicular extract of, on deciduomata..638
— insufficiency and mental disorders 642
— luteinization of, by combined anterior pituitary and pregnancy urine extracts 513
— new procedure for detection of follicular hormone of.....705
— of foetal horses as hormone source 638

Ovary, possible relation of follicular cysts of, to uterine fibroids.432
— powdered follicular extract of, and estrus 639
— reaction of, to hypophysis and pregnancy urine extracts ...639
— relation of gonadotropic hormone of hypophysis to.....643
— — — hypertrophy to hormone of 428
— resection and masculinization in guinea pigs 748
— response of, to pregnancy urine extracts 640
— — to prolan and anterior lobe extract 298
— stimulating extract from blood of pregnant women 148
— stimulation and hypophysis...293
— — of, by adrenal extracts.....249
— structure of, and hysterectomy.291
— transplantation 290
— — and mammary region pigmentation 288
— transplants and male reproductive system 150
— tumor of and secondary sex changes 642
Ovulation and hypophysis 206
— effect of ovary extract on.....427
— mechanism of, in rabbit.....747
— production of, by gonadotrophic extracts 714
— time in monkey 747
Oxygen consumption rate, effect of irradiated ergosterol on....303

Pancreas ablation and hypophysis.159
— — effect of on nitrogen metabolism 643
— adenoma of 157
— and cirrhosis of liver.....280
— — hypophysis sex hormone...426
— — — relationship of 649
— — muscle glycogen recovery..757
— — — restorage 757
— — ovary, relationship of.....442
— — pain stimuli 302
— depressor substance in.....455
— diabetes, effect of adrenal medulla and thyroid on respiratory metabolism of 159
— disorders in the Southeast....221
— internal and external secretions of 301
— islet cell tumor of, and insulin content 649
— ligation of tail of, and sugar tolerance 760
— radiation of region of, and insulin secretion 759
Pancreatic diabetes and adrenal insufficiency 652
Parathyreotropic action of anterior pituitary 350
Parathyroid ablation and experimental cancer 742
— — — osteitis fibrosa cystica...761
— activity, contribution to knowledge of 761
Parathyroid and blue sclera.....427
— — sodium fluoride poisoning..657
— dysfunction, report of a case..657
— extract and body temperature.303
— — — ergosterol, use of.....657
— — — heart efficiency 303
— — — oxygen consumption rate.303
— — — scleroderma 304
— — — sugar tolerance 651
— — — vagal innervation 447
— — effect of diet on response.. to 655, 656
— glands, effect of anterior lobe extracts on 350
— — in man, number and location of 654
— — physiology of 760
— hormone action, mechanism of.304
— — — of, on calcium metabolism 762
— — and osteitis fibrosa.....160
— — assay of 302
— — chemical studies on.....657
— — effect of, on bony system of young rat 303
— — — — — calcium and phosphorous metabolism 303
— — — — — content of human milk ...159
— — in abnormal uterine bleeding 653
— — — blood of pregnant women.446
— — — rachitic animals 654
— influence of extirpation of one on lipoid content of corresponding undisturbed gland.657
— tetany and guanidine concentration 159
— — case of, with normal chronaxie and gastric spasms.656
— tissue within the thymus.....397
— transplant for tetany.....304
— tumors and hyperparathyroidism 761
— — — osteitis fibrosa 160
Pars intermedia, action of hormone of 299
Physiology of prostate 123
Pineal calcification and other endocrine disturbances 304
— extracts, therapeutic use of...304
— function of 625
Pitocin, use of, in labor.....211
Pituitary headache 596
— implants in adult males..... 86
Placenta, chemical nature of extract of 71
— enzymes of, in pregnancy.....284
— relation between extracts of, and anterior lobe extracts...639
Polydactylism, rare case of.....155
Pregnancy, accuracy of rabbit ovulation as test for.....432
— and changes in blood composition 290
— — corpus luteum extract.....745
— — hormone concentration in skin 429
— — nitrogen metabolism 428
— — thyroid function 313
— — uterine activity 748

Pregnancy cells in hypophysis and reproduction 288
— changes in anterior hypophysis.647
— — of islets of Langerhans in.649
— delayed 286
—.diagnosis, Friedman's reaction.285
— effect of hypophysis ablation on 749
— — — on hypophysis 721
— Friedman modification of test for 547
— hormone diagnosis of viability of 431
— hormones of 432
— hypophysectomy during 646
— lactation and hypophysis ablation during 237
— metabolism in 759
— new test for diagnosis of.....641
— oxytocic factors in blood of...746
— -prolan and reproductive system 601
— — — reproductive system 607
— pseudo-induction by experimental hyperthyroidism ...766
— reaction in mares.....549
— recovery of gonadotropic substances from urine of 1
— relation between extracts of blood and urine of and hypophysis extracts 639
— relation of corpus luteum to gravid uterus in.....747
— test 288
— — new method of.....749
— toxicosis and posterior lobe hormones 746
— urine and sex determination...521
— — effect of extracts of, on parathyroid glands 350
— — — — on growth.....482
— — extracts and corpus luteum.287
— — — — hypophysis 441
— — — — ovary luteinization ..513
— — — — production of deciduomata 430
— — — — sex underdevelopment 47
— — — — testicular descent ...475
— — — — uterine bleeding 431
— — — effect of, on hyperthyroidism 113
— — — — — — hypophysis 640
— — — — — — immature ovary.429
— — — — — — sex organs 641
— — — ovary response to.....640
— — — potency of 211
— — — reaction of ovaries to...639
— — gonadotrophic principle of, and gaseous metabolism.642
— — hormone and adult ovary..437
— — menstrual response to extracts of 203
— — quantitative observations on action of extracts of.....747
— Voge bromine tests of urine for.749
Progestin and human corpus luteum 667
Prolactin, clinical use of..... 18
Prolan and blood sugar.....650
— — hyperglycemia 382
— — tumor growth 300
— effect of, on growth.....482
Prolan in urine during senility...554
Prostate, physiology of 123
Protein metabolism and thyroid ablation 308
— — influence of gonads on.....290
Pseudo-hermaphroditism, case of.745
Pubertas praecox and pineal function 625
Puberty, effect of splenectomy on.762
— physiology of 755

Reproduction and parathyroid ablation 655
Roentgen radiation of testes and prostate 123
— therapy of exophthalmic goiter.591

Schizophrenia, reaction of adrenal extract in 576
Secondary sex characters, effect of fuel oil on 285
Secretin concentrate and hemoglobin in circulating blood.....188
Senility, anterior lobe hormone in urine during 554
Sex activity and anterior lobe extract 296
— and internal secretions 423
— antagonism and ovary grafts in males 640
— changes, ovarian tumor and secondary 642
— characteristics in mammals, experimental production of...748
— cycle, effect of pineal implants on 625
— — in human female.....550
— development and adrenal cortex 741
— determination test of Dorn and Sugarman 521
— function and adrenal glands...256
— gland hormones and gonadotropic hormone of hypophysis 751
— hormones, influence of on creatine metabolism 427
— — of anterior lobe of hypophysis 435
— — standards for 149
— — use of, in disturbed estral cycle 549
— — uterine reactions to.....539
— inversion, studies on.....150
— organs, effect of anterior lobe and pregnancy urine extracts on 641
— periodicals on endocrinology of.421
— underdevelopment and pregnancy urine extract 47
Sexual maturation and thyroid feeding 308
— — effect of feeding thyroid on.450
Specific dynamic action and thyroid-hypophysis ablation.....752
— — — influence of pituitary on.409
Spermatogenesis, effects of pituitary implants on..... 86
Spleen ablation and iron excretion.306
— — — puberty 762

Spleen ablation and tumor growth.742
— extract and cell permeability..281
— the hormone of 447
Sporadic goiter and other thyroid disorders 306
— — inheritance of 660
Sterility and thyroid extract.....211
— — x-ray irradiation 148
— effect of prolan B injections on.639
Stomach hormone and pernicious anemia 426
Sugar tolerance and insulin in thin people 756
— — surgical attempts to increase 760
Sympathetic stimulation, humoral effects of 633

Testes, action of sex hormone of hypophysis on 753
— and gonad-stimulating principle of anterior lobe.....123
— biology of 423
— descent of, in macque and chimpanzee 643
— embryonal carcinoma of, in pseudohermaphrodite 152
— extract and cell permeability..281
— — — tissue permeability 150
— gonadotropic hormone in urine of case of teratoma of.....629
— influence of anterior lobe hormone on metabolism of.....440
— of foetal horses as hormone source 638
— pathologic physiology of teratoma 746
— physiology of 142
— reaction in sex determination test 521
— weight of 284
Testicular descent, effect of pregnancy urine extract on 475
Thymus ablation and experimental cancer 742
— and adrenal antagonism.....305
— — insanitary conditions 453
— extract and growth.....657
— parathyroid tissue within.....397
Thyreotropic extracts of anterior lobe of hypophysis 645
Thyroid ablation and angina pectoris 306
— — — anterior lobe extract....752
— — — basal metabolic rate of rabbit 311
— — — cardiovascular disease ..448
— — — effect of anterior lobe extract on metabolism..752
— — — eye reactions 652
— — — feeding in snakes.....453
— — — glucose administration..453
— — — insulin resistance 643
— — — keratosis 441
— — — physico-chemical changes in plasma 314
— — — protein metabolism 308
— — effect of, on diabetes mellitus 455

Thyroid ablation in treatment of angina pectoris 765
— action of fluorine on histological aspect of 453
— — — — hypophysis anterior lobe extract on weight and histology of 645
— activity, relation of, to hypophysis 434
— and anterior lobe extract.....293
— — arthritis 308
— — blood disorders 636
— — blue sclera 427
— carbohydrate metabolism 454
— — cirrhosis of liver 280
— — diabetes 75
— — eclampsia 312
— — gonad-stimulating hormone.156
— — hypophysis 291, 295, 310, 315, 438, 551, 660, 662
— — — activity in relation to basal metabolism 660
— — — extract 451
— — — relation of, to molting...743
— — — sex hormone 426
— — insanitary conditions 453
— — iodine metabolism 450
— — liver damage 664
— — muscle metabolism 543
— — ovary 548
— — pineal extracts 304
— — reproductive glands 282
— — respiratory metabolism of diabetes 159
— at base of tongue, case report..453
— compensatory hypertrophy of, and hypophysis 660
— constituents, calorigenic action of 317
— disease and acid-base equilibrium 307
— — — phagocytosis 305
— — blood cholesterol in.....660
— disorders in childhood 764
— — — the Southeast 221
— dysfunction, gastric acidity in.766
— effect of anterior lobe extract of hypophysis on 658
— — — — — — — on weight of...294
— — — carbohydrate and protein diet on hormone content of 314
— — — cod-liver oil on.....254
— — — experimental diets on....197
— — — feeding of 450
— — — gonad ablation on.....744
— — — haloid salts on weight and structure of.....170
— — — hypophysis treatment upon 415
— — — insulin on 663
— — — luteinizing and follicular extracts of hypophysis on 436
— — — rachitogenic diets on....316
— — — sunlight and darkness on.452
— — — thyroid-stimulating hormone of hypophysis on.643
— enlargement in school children.657
— extirpation and milk secretion.659
— extract and albumin-globulin ratio 147

Thyroid extract and blood cholesterol 665
——— sugar 437
——— cholesterol 315
——— dwarfism 387
——— excretion of thyroid gland hormone 763
——— fat distribution 150
——— growth 657
——— hormone in skeletal growth 441
——— metabolism 307
——— in cretins 451
——— myxedema 664
——— personality changes 453
——— protective substance in blood and tissues 762
——— sodium chloride content of bile 283
——— sperm motility 546
——— sugar tolerance 651
——— tissue metabolism 746
——— tumor growth 309
—— effect of alkali on absorption of 665
——— on adrenal 636
——— basal metabolism .228
—— in treatment of whooping cough 739
——— uterine bleeding 148
—— mode of action of.....765
—— response of feather follicle to 546
—— use of, in menstrual irregularity and sterility.....211
— feeding and blood flow.....310
——— iodine in tissues 762
——— pseudo-pregnancy 766
——— sexual maturation.....308
— function and iodine content of blood 658
—— during pregnancy.....313
—— estimation of 311
—— of mothers, relation of, to infant birth weight.....453
—— relation of basal metabolic rate and suspension stability of blood to 765
— gland activity and lack of oxygen 663
—— deficiency in chronic arthritis 451
—— effect of tracheal compression 658
—— estimated thyroxine in 310
—— in normal adults in North America 659
—— preparation, standardization of 314
—— removal and heart disease..693
—— weight in Belgian low-lands.659
— histogenesis of 309
— hormone, excretion of, after dried thyroid feeding.....763
—— in experimental hyperthyroidism 313
— influence of on genital function.423
— insufficiency and familial infantilism 533
Thyroid insufficiency, iodine tolerance test for.....487
— iodine and bromine content of.663
—— content of.....661
— lymphoma of 452
— metabolic studies on.....314
— preparations, standardization of 315
— relation of, to anterior lobe of hypophysis 552
——— hypophysis 434
——— ovary 431
— seasonal variation in size of...283
— size of, in Freiburg students..313
— stimulating hormone of anterior lobe of hypophysis.....645
——— hypophysis and fat metabolism 505
— structure of blood vessels in...662
— treatment and basal metabolism 764
—— in optic nerve neuritis.....527
— use of desiccated substance, in case of Laurence-Moon-Biedl syndrome 583
— weight of 284
Thyroiditis, report of a case.....454
Thyroparathyroid ablation and blood chemistry 654
——— oestrus 654
——— skeletal growth 441
——— tumor tissue grafts 743
—— effect of, on growth, reproduction and lactation ...655
Thyrotoxicosis, diagnostic use of iodine in 765
— simulating primary neurosis...659
Tissue respiration and adrenal function 179
Tumor growth and anterior pituitary hormone 191

Urine, normal and hyperglycemia.382
Uterus, activity of, during pregnancy and parturition 748
— as organ of internal secretion.548
— dysfunctional bleeding of and pregnancy urine extract....431
— effect of anterior pituitary-like hormone on irregular bleeding of 551
— implants of carcinoma in, effect of, on hypophysis 436
— influence of on ovary 642
— parathyroid hormone and calcium in abnormal bleeding of 653
— reaction of, to sex hormone...539
— removal and structure of ovary.291

Virility and hirsutism, pathology of 429

Water metabolism and posterior pituitary extract 439